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Orofacial Clefts in the National Birth Defects Prevention Study, 1997-2004

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Abstract

Orofacial clefts are among the most common types of birth defects, but their clinical presentation has not been well described in a geographically diverse US population. To describe the birth prevalence and phenotype of nonsyndromic clefts, we used data from the National Birth Defects Prevention Study (NBDPS), a multi-site, population-based, case-control study aimed at identifying genetic and environmental risk factors for birth defects. Included in the study were infants born during 1997-2004 with a cleft lip (CL), cleft lip with cleft palate (CLP), or cleft palate (CP). Infants with clefts associated with recognized single-gene disorders, chromosome abnormalities, holoprosencephaly, or amniotic band sequence were excluded. A total of 3,344 infants with nonsyndromic orofacial clefts were identified, including 751 with CL, 1,399 with CLP, and 1,194 with CP, giving birth prevalence estimates of 0.3, 0.5, and 0.4/1,000 live births, respectively. Among infants with CLP where cleft laterality was specified, about twice as many had unilateral vs. bilateral involvement, while for CL there were over 10 times as many with unilateral vs. bilateral involvement. Involvement was most often left-sided. About one-quarter of infants with CP had Pierre Robin sequence. Over 80% of infants had an isolated orofacial cleft. Among infants with CL or CLP, heart, limb, and musculoskeletal defects were most commonly observed, while heart, limb, and central nervous system defects were most common among infants with CP. Better understanding of the birth prevalence and phenotype may help guide clinical care as well as contribute to an improved understanding of pathogenesis.

Keywords

cleft lip; cleft palate; congenital abnormalities; prevalence; birth defects

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Introduction

Orofacial clefts are among the most common congenital defects [Canfield et al., 2006]. Orofacial clefts are usually classified as either cleft lip with or without cleft palate (CL+/-P) or cleft palate only (CP), and these phenotypes are believed to be etiologically distinct, based on differences in embryological development and epidemiologic characteristics [Spritz, 2001; Murray, 2002]. Although CL+/-P can be subdivided into cleft lip only (CL) and cleft lip with cleft palate (CLP), most epidemiologic studies analyze them as a single group because they are generally considered to be pathogenetically similar. In the United States, others have estimated that CL+/-P affects 1.05 per 1,000 live births and CP affects 0.63 per 1,000 live births [Canfield et al., 2006]. Previous work has shown that in as many as three-quarters of infants with CL+/-P and about half of those with CP, the orofacial cleft is an isolated defect; that is, the defect is not associated with other unrelated major birth defects, single-gene disorders, or chromosome abnormalities [Croen et al., 1998].

The birth prevalence of orofacial clefts varies depending on several factors, including infant sex, race/ethnicity, and maternal age. Past studies have found that the birth prevalence of CL +/-P is 2-fold higher among males, while CP is 1.5 times more prevalent among females [Shaw et al., 1991; Hashmi et al., 2005]. Previous work has consistently shown a lower birth prevalence of orofacial clefts among non-Hispanic Blacks, compared to non-Hispanic Whites [Croen et al., 1998; Tolarova and Cervenka, 1998; DeRoo et al., 2003; Hashmi et al., 2005; Canfield et al., 2006]. For maternal age, it has been shown that both older and younger mothers are at increased risk for having a child with an orofacial cleft when compared to the referent group of 25- to 29-year-olds, even when infants with chromosome abnormalities are excluded [Shaw et al., 1991; DeRoo et al., 2003; Reefhuis and Honein, 2004]. Studies have also examined associations between orofacial clefts and other fetal outcomes. Some studies have shown that both CL+/-P and CP were associated with low birth weight (< 2500 g) [Mili et al., 1991; Wyszynski et al., 2003]. Others have found that preterm infants were more than two times as likely than term infants to have CL+/-P or CP; however, when infants with isolated CL+/-P or CP (infants with no other unrelated major defects, single-gene disorders, or chromosome abnormalities) were examined separately, this association was not observed [Rasmussen et al., 2001; Shaw et al., 2001].

Clefts have a complex etiology and likely result from an interaction between environmental and genetic factors [Murray, 2002]. Smoking has been identified as the most consistent environmental risk factor with odds ratios of 1.3 and 1.2 for CL+/-P and CP, respectively, based on a recent meta-analysis [Little et al., 2004]. Analysis of the association between maternal smoking and orofacial clefts using data from the National Birth Defects Prevention Study, a large, multi-site case-control study and the source of the data in the current study, found nearly identical findings (odds ratios of 1.3 and 1.2 for CL+/-P and CP, respectively) [Honein et al., 2007]. Genetic contributions are also being increasingly recognized with the most established contributor being variants in the *IRF6* gene [Zucchero et al., 2004]. Despite the recent progress in identifying environmental and genetic risk factors for orofacial clefts, major gaps in knowledge remain.

The present study was based on data from the NBDPS, established in 1997 to facilitate the investigation of risk factors for birth defects, including orofacial clefts. These data were used to examine the birth prevalence of orofacial clefts overall and within several clinical and demographic subgroups, as well as to better describe the phenotype of orofacial clefts, including the types of major defects associated with their occurrence. These observations may help to improve our understanding of factors that play a role in the occurrence of

orofacial clefts, aid in the development of public health prevention efforts, and provide information useful to clinicians caring for infants with orofacial clefts.

Materials and Methods

Descriptive Epidemiologic Study of Orofacial Clefts

The NBDPS is an ongoing, population-based, multi-site, case-control study of major birth defects, including orofacial clefts. Detailed methods have been described elsewhere [Yoon et al., 2001]. To maximize the likelihood of identifying risk factors for nonsyndromic birth defects, the NBDBS excludes infants with birth defects that occur as part of syndromes (i.e., infants with single-gene disorders or chromosome abnormalities). The NBDPS provides a unique opportunity to describe nonsyndromic orofacial clefts using population-based data collected using a consistent case definition. Data on infants with birth defects are collected through population-based birth defects surveillance systems in ten sites: Arkansas, California, Centers for Disease Control and Prevention (CDC - Atlanta, Georgia), Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Each site received institutional review board approval for this study.

In the NBDPS, infants include live births (all centers), fetal deaths ≥ 20 weeks (Arkansas, California, Iowa, Massachusetts, Texas, North Carolina, and CDC), and elective pregnancy terminations (Arkansas, California, Iowa, Texas, and CDC). For this analysis we included infants with a date of birth on or after October 1, 1997 and an estimated date of delivery (EDD) on or before December 31, 2004. Clinical information was reviewed by one of four clinical geneticists (to enhance diagnostic comparability for these analyses and to classify the infant as having an isolated cleft [no additional unrelated major defect] or multiple defects [one or more unrelated major defects in addition to the cleft]) [Rasmussen et al., 2003]. Infants with CL and CLP were analyzed separately for several demographic factors, and statistical tests were performed for two variables: whether infants had additional, unrelated major defects or not, and whether involvement was unilateral or bilateral. Infants with CP diagnosed as Pierre Robin sequence [Printzlau and Andersen, 2004] are included in the analyses of CP in the NBDPS. In Pierre Robin sequence, the initial event, mandibular hypoplasia, keeps the tongue high in the oral cavity, causing a cleft in the palate by preventing the closure of the palatal shelves. Because of the difficulty of making a diagnosis of Pierre Robin sequence based on abstracted clinical data, infants were classified as having Pierre Robin sequence only if clinical information abstracted from medical records noted the presence of this phenotype.

Our study included nonsyndromic orofacial clefts — orofacial clefts of unknown etiology with and without associated, unrelated major congenital defects. These defects were documented by physical examination and/or autopsy and we excluded infants whose diagnosis was made only on prenatal ultrasonography without postnatal confirmation. Also excluded were orofacial clefts secondary to another defect (e.g., holoprosencephaly or amniotic band sequence); infants described as having microform CL, pseudocleft lip, or submucous CP because these defects might be incompletely ascertained [Thomson and Delpero, 1985]; and infants with lateral or oblique facial clefts because they are believed to be pathogenetically distinct from typical orofacial clefts [Stelnicki et al., 1997].

We calculated the birth prevalence, prevalence ratios (PRs), and 95% confidence intervals (CIs) for orofacial clefts (CL, CLP, and CP) by infant sex, maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other), maternal age in years (<20, 20-24, 25-29, 30-34, 35-39, ≥40), gestational age for live born singletons only (preterm [<37 completed weeks], term [≥37 completed weeks]), birth plurality (singleton, twins or higher), month of conception, site of maternal residence, and year of EDD. All data on case infants

for these demographic variables were derived from the NBDPS clinical database. We derived the birth prevalence estimates from the number of affected infants per 1,000 live births in the source population from which the infants were ascertained. The Statistical Analysis Battery for Epidemiologic Research [Centers for Disease Control and Prevention, 2008] was used to calculate 95% CIs for the PRs, using the Taylor Series method. Month of conception was calculated by subtracting 266 days from the EDD abstracted from the medical records. For those infants without an EDD abstracted from their medical records, we used the date of birth as the EDD and subtracted the gestational age (in days). We also calculated the frequencies of CL and CLP by laterality (bilateral vs. unilateral, left, right, or midline), and for CP, we examined the presence or absence of Pierre Robin sequence. A Chi-square analysis was done to assess any difference in the proportion of isolated and multiples between CL and CLP. Chi-square analysis was also conducted to assess any difference in the proportion of unilateral and bilateral clefts between CL and CLP. These analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC). Values of $p < 0.05$ were considered statistically significant.

To determine the most common additional major defects observed with orofacial clefts, we reviewed the NBDPS data for infants with orofacial clefts that were classified as having multiple major defects [Rasmussen et al., 2003] and calculated the frequencies of individual defects.

Supplemental Surveillance Study

To determine the proportion of all infants with orofacial clefts that met the case inclusion criteria for the NBDPS, we compared infants with CL, CLP, or CP who were eligible and included in the NBDPS to all infants with orofacial clefts who were ascertained by the population-based birth defects surveillance systems in two sites: CDC's Metropolitan Atlanta Congenital Defects Program (MACDP) and the California Birth Defects Monitoring Program (CBDMP). Detailed information about these surveillance systems has been previously described [Croen et al., 1991; Correa et al., 2007]. To identify infants with orofacial clefts in the two surveillance systems, we used the modified 6-digit codes, based on the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD9-CM) and British Paediatric Association coding classification systems [Correa et al., 2007] for CL (749.100-749.120, 749.190), CLP (749.200-749.290) and CP (749.000,-749.070, 749.090). We determined the proportion of infants with orofacial clefts that did not meet the case definition for NBDPS, and the specific reasons for exclusion (e.g., single-gene disorders, chromosome abnormalities, microform cleft lip, cleft uvula).

Results

Descriptive Epidemiologic Study of Orofacial Clefts

A total of 3,344 infants with nonsyndromic orofacial clefts meeting the NBDPS case definition was identified and included: 751 (22%) with CL, 1,399 (42%) with CLP, and 1,194 (36%) with CP. The birth prevalence was 0.3/1,000 live births for CL, 0.5/1,000 live births for CLP, and 0.4/1,000 live births for CP. The majority of infants in the NBDPS (92% of infants with CL, 85% of infants with CLP, and 79% of infants with CP) were classified as having isolated defects. Among those infants with specified laterality, about twice as many infants with CLP had unilateral vs. bilateral involvement while for CL, there were over 10 times as many with unilateral vs. bilateral involvement. For both CL and CLP, involvement was most often left-sided (Table I). Among infants with CP, 264 (22%) had cleft of the hard palate, 519 (43%) had cleft of only the soft palate, and in 411 (34%), the palatal involvement was not specified. About one-quarter of infants with CP had Pierre Robin sequence. Among infants with Pierre Robin sequence, 90 (32%) had cleft of the hard palate, 90 (32%) had cleft

of only the soft palate, and in 99 (35%), the palatal involvement was not specified. Among infants without Pierre Robin sequence, 174 (19%) had cleft of the hard palate, 429 (47%) had cleft of only the soft palate, and in 312 (34%), the palatal involvement was not specified.

The birth prevalence of CL and CLP were lower among females than among males (PR= 0.7 (0.6-0.8) and 0.5 (0.5-0.6), respectively), whereas the birth prevalence of CP was higher among females with a PR = 1.2 (1.1-1.4). When compared to non-Hispanic Whites, the birth prevalence of all cleft types was lower among non-Hispanic Blacks, while the birth prevalence was lower only for CL and CP for Hispanics. The birth prevalence of CLP was lower among mothers aged 30-34 years compared to mothers aged 25-29 with a PR = 0.8 (0.7-0.9). Preterm birth (20-36 weeks gestational age) was associated with CLP and CP with a PR = 1.4 (1.2-1.6) and 1.8 (1.5-2.1), respectively. Birth prevalence estimates varied by month of conception and study site for all cleft types, but no clear pattern emerged. (Table II). We also assessed CP with and without Pierre Robin sequence to determine if there were differences by clinical and demographic characteristics. The diagnosis of Pierre Robin sequence differed significantly by study site from a low of 12.9% of CP in Texas to a high of 31.9% of CP in Massachusetts. The diagnosis of Pierre Robin sequence was also more common in infants of non-Hispanic white mothers (25.4%) than infants of non-Hispanic black mothers (16.8%) or Hispanic mothers (18.8%), and was less common among infants of mothers < 20 years of age than mothers of any other age group.

The most common additional major defects among infants with CL were heart defects (3.3%), limb defects (1.6%), and musculoskeletal defects (1.5%). The same types of defects were the most commonly observed in infants with CLP, but their frequency was higher: heart (7.2%), limb (3.6%), and musculoskeletal defects (3.1%). Defects involving the heart (9.1%), limbs (6.3%), and central nervous system (CNS) (6.2%) were most common for CP (Table III).

Supplemental Surveillance Study

Of the 1,291 infants with orofacial clefts identified by birth defects surveillance systems in metropolitan Atlanta and California, 958 were included in the NBDPS. A total of 333 infants were excluded (50 with CL, 122 with CLP, 157 with CP, and 4 with lateral facial clefts). Of these, 324 were excluded because they did not meet the NBDPS cleft case definition and 9 were inappropriately excluded (Table IV). Thus, based on evaluation at these two sites, 74% of infants with orofacial clefts are included in the NBDPS. The most common reasons for exclusion from NBDPS were chromosome abnormalities (50%) and single-gene disorders (18%) (Table IV). The most common chromosome abnormalities observed were trisomy 13, trisomy 18, and 22q11.2 deletion. For single-gene disorders, the most commonly observed were van der Woude and Stickler syndromes.

Discussion

This study is the first to describe the epidemiology of all eligible infants with apparently nonsyndromic (infants without a recognized or strongly suspected chromosome abnormality or single-gene disorder) orofacial clefts (both with and without a completed maternal interview) in the NBDPS, the largest population-based, case-control study of major birth defects ever conducted in the United States. The NBDPS has a consistent case definition across the 10 geographic sites contributing data to the study. By excluding infants with single-gene disorders and chromosome abnormalities, a case group with less etiologic heterogeneity is created that hopefully maximizes opportunities for identifying risk factors. Based on two of the ten sites examined, approximately 70% of all orofacial clefts

ascertained by birth defects surveillance systems in the included study sites met the NBDPS case definition for orofacial clefts.

While CL and CLP have often been considered pathogenetically similar and grouped into the category of CL+/-P, this large multi-site study afforded the opportunity to examine the descriptive epidemiology of CL and CLP separately. Some of our results show that CL and CLP share certain epidemiologic characteristics (e.g., higher birth prevalence in males, lower birth prevalence in Non-Hispanic Blacks), but others support the hypothesis that these two anomalies may be distinct [Harville et al., 2005]. CL and CLP differed significantly in the proportion of defects that were unilateral and bilateral, with CLP showing a larger proportion of bilateral defects, an observation that has been previously reported [Hagberg et al., 1998]. Although the same types of associated defects were most commonly associated with CL and CLP, our data confirmed previous observations that associated major defects are more frequent among cases with CLP than among cases with CL [Tolarova and Cervenka, 1998; Stoll et al., 2000; Harville et al., 2005]. One explanation for these findings is that these two defects might be pathogenetically distinct and thus, should be analyzed separately in future investigations, a concept supported by an epidemiologic study [Harville et al., 2005] and by recent biological data that suggests that isolated cleft lip in humans can be influenced by specific genetic variants [Rahimov et al., 2008]. Among other possible explanations is that these defects have a common pathogenetic origin and that clefts involving both the lip and palate represent a more severe expression of the defect than those involving only the lip. Thus, they are more likely to be associated with more severe manifestations, that is, more likely to have bilateral involvement and to have additional, unrelated major defects.

The NBDPS data are consistent with other studies showing that CL and CLP are more prevalent among males, while CP is more prevalent among females [Tolarová, 1987; Shaw et al., 1991; Hagberg et al., 1998; DeRoo et al., 2003; Forrester and Merz, 2004; Hashmi et al., 2005]. Our data also confirm past work that show that the birth prevalence of all types of orofacial clefts is lower among non-Hispanic Blacks when compared to non-Hispanic Whites and that CP is less common among Hispanics [Croen et al., 1998; Tolarova and Cervenka, 1998; Hashmi et al., 2005]. We also found that the birth prevalence of CL is significantly lower among Hispanics compared to Non-Hispanic Whites, a novel finding.

Our results for maternal age did not show a statistically significant difference in birth prevalence except for the 30- to 34-year-old group. For this age group, the birth prevalence was lower for CLP. Previous work has suggested that CL [Reefhuis and Honein, 2004] is associated with younger maternal age (<20), which we did not confirm. Other studies found increased odds of having an infant with CP with older maternal age (>30) [Shaw et al., 1991; Hashmi et al., 2005], which we also did not confirm. Although previous studies have shown that prematurity is associated with a higher birth prevalence of CP [Rasmussen et al., 2001; Shaw et al., 2001], we observed this association for both CLP and CP. Significant differences for CP with and without Pierre Robin sequence were noted by study site and maternal ethnicity, but this likely reflects differences in clinical practice and terminology between sites rather than etiologic differences.

In our study, the most common defects associated with CL and CLP were heart, limb, and musculoskeletal defects. For CP, heart, CNS, and limb anomalies were most commonly observed. It is plausible that heart defects and orofacial clefts are frequently seen with one another as a result of the intertwined embryological development of the heart and face. The aortic arches of the primitive heart surround the pharyngeal arches from which the face forms. Given that heart defects are one of the most common birth defects [Correa et al., 2007], it is not surprising that this group of defects is the one most commonly observed in

infants with orofacial clefts. However, our results showed that infants with orofacial clefts have a higher birth prevalence of heart defects than infants without a cleft for whom the birth prevalence is <1% [Botto et al., 2001] and that CNS anomalies were one of the most common types of defects seen in infants with CP. Several studies have shown that individuals with isolated orofacial clefts have abnormalities in brain structure, which can be associated with neurodevelopmental disorders [Nopoulos et al., 2002; Nopoulos et al., 2007]. Clinicians caring for infants with clefts should be aware of these observations and maintain a high index of suspicion that can lead to early detection and intervention for these conditions.

There are several strengths of this study. First, this is the largest study of infants with orofacial clefts ever conducted in the United States. In addition, infants are ascertained from population-based birth defects surveillance systems that include detailed clinical information abstracted from medical records on the cleft phenotype and associated defects. The multi-site and multi-year nature of these data have allowed us to have sufficient sample size to divide orofacial clefts into three more homogeneous phenotypes: CL, CLP, and CP, important because of growing evidence that CL might be distinct from CLP [Spritz, 2001; Murray, 2002; Harville et al., 2005]. The data are from 10 geographic sites in the United States, providing ethnic and socioeconomic diversity. This is the first study to capture this much of the US population using such a rigorous data collection approach. Finally, clinical information on all infants was reviewed by clinical geneticists to assure adherence to the case definition and careful classification.

This study had several limitations. Despite including infants from varied geographic locations, some racial and ethnic groups did not reflect the US population, limiting generalizability. Non-Hispanic Blacks and Asians account for 12% and 4% of the total US population, respectively, [Grieco and Cassidy, 2001] but comprised only 8% and <1% of our sample, partially due to the lower birth prevalence of orofacial clefts among non-Hispanic Blacks as compared to non-Hispanic whites. Hispanics account for 13% of the total US population but made up 25% of our sample. Another limitation is that some infants with single-gene conditions or chromosome abnormalities might have been inadvertently included in our study. Clinical geneticists reviewed abstracted data from medical records on infants with clefts and excluded infants with recognized or strongly suspected single-gene conditions or chromosome abnormalities. However, some of these conditions may have a subtle phenotype (e.g., 22q11.2 deletion or Stickler syndrome), and thus these infants might not have been recognized as affected by the examining clinician. Although some infants with these more subtle phenotypes were appropriately excluded from our study (Table 4), others are likely to have been included. Another limitation is that the quality of clinical data may have varied depending on its source and the type of health care provider performing the physical exam on the infant.

Several factors, including infant sex, maternal race-ethnicity, maternal age, and gestational age, were associated with nonsyndromic orofacial clefts in our study. Our ability to describe orofacial clefts by CL, CLP, and CP has provided further evidence that these cleft phenotypes may be etiologically distinct, and therefore, should be examined separately, when possible. Also, our analysis of additional defects underscores the need for infants with orofacial clefts to be carefully examined for other major congenital abnormalities.

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TABLE I

Classification of Orofacial Clefts by Defect Status and Laterality, National Birth Defects Prevention Study, 1997-2004

Clinical Presentation	CL (N = 751) N (%)	CLP (N = 1,399) N (%)	CP (all) (N = 1,194) N (%)	CP with Pierre Robin sequence[e] (N = 279) N (%)	CP without Pierre Robin sequence[e] (N = 915) N (%)
Isolated	691 (92) [a,b]	1,185 (85) [a,c]	942 (79)[b,c]	216 (77)	726 (79)
Multiple	60 (8) [a,b]	214 (15) [a,c]	252 (21)[b,c]	63 (23)	189 (21)
Bilateral	56 (7)[d]	423 (30)[d]	n/a	n/a	n/a
Unilateral	599 (80)[d]	844 (60)[d]	n/a	n/a	n/a
Unilateral, Right	209 (35)	291 (34)	n/a	n/a	n/a
Unilateral, Left	372 (62)	502 (59)	n/a	n/a	n/a
Unilateral, NOS	18 (3)	51 (6)	n/a	n/a	n/a
Midline	10 (1)	9 (1)	n/a	n/a	n/a
NOS	86 (11)	123 (9)	n/a	n/a	n/a

[a] Chi-square analysis comparing proportion of isolated and multiple defects between CL and CLP ($p < 0.01$).

[b] Chi-square analysis comparing proportion of isolated and multiple defects between CL and CP ($p < 0.01$).

[c] Chi-square analysis comparing proportion of isolated and multiple defects between CLP and CP ($p < 0.01$).

[d] Chi-square analysis comparing proportion of unilateral and bilateral defects between CL and CLP ($p < 0.01$).

[e] Pierre Robin sequence is determined by diagnosis and notation in the medical record by the clinician providing care to the infant/child.

TABLE II

Birth Prevalence of Orofacial Clefts by Clinical and Demographic Characteristics, National Birth Defects Prevention Study 1997-2004

		CL			CLP			CP		
	Total Births	Cases	Prev.[a] (/1,000)	PR (95% CI)	Cases	Prev.[a] (/1,000)	PR (95% CI)	Cases	Prev.[a] (/1,000)	PR (95% CI)
Infant Sex										
Male	1396906	462	0.3	Ref	921	0.7	Ref	548	0.4	Ref
Female	1334903	288	0.2	0.7 (0.6-0.8)	474	0.4	0.5 (0.5-0.6)	644	0.5	1.2 (1.1-1.4)
Maternal Race-Ethnicity										
Non-Hispanic White	1508215	466	0.3	Ref	769	0.5	Ref	774	0.5	Ref
Non-Hispanic Black	349561	58	0.2	0.5 (0.4-0.7)	106	0.3	0.6 (0.5-0.7)	101	0.3	0.6 (0.5-0.7)
Hispanic	719501	174	0.2	0.8 (0.7-0.9)	419	0.6	1.1 (1.0-1.3)	234	0.3	0.6 (0.5-0.7)
Other	158339	52	0.3	1.1 (0.8-1.4)	94	0.5	1.2 (0.9-1.5)	79	0.5	1.0 (0.8-1.2)
Maternal Age (years)										
<20	307970	84	0.3	1.1 (0.8-1.4)	186	0.6	1.2 (1.0-1.5)	125	0.4	1.0 (0.8-1.2)
20-24	650828	201	0.3	1.2 (1.0-1.5)	391	0.6	1.2 (1.0-1.4)	278	0.4	1.0 (0.9-1.2)
25-29	715000	183	0.3	Ref	355	0.5	Ref	305	0.4	Ref
30-34	662100	182	0.3	1.1 (0.9-1.3)	264	0.4	0.8 (0.7-0.9)	276	0.4	1.0 (0.8-1.2)
35-39	326804	83	0.3	1.0 (0.8-1.3)	164	0.5	1.0 (0.8-1.2)	166	0.5	1.2 (1.0-1.4)
≥40	68398	16	0.2	0.9 (0.5-1.5)	30	0.4	0.9 (0.6-1.3)	35	0.5	1.2 (0.9-1.7)
Gestational Age										
20-36 weeks	272369	54	0.2	0.7 (0.6-1.0)	175	0.6	1.4 (1.2-1.6)	185	0.7	1.8 (1.5-2.1)
≥37 weeks	2398849	646	0.3	Ref	1108	0.5	Ref	922	0.4	Ref
Plurality										
Singleton	2640508	725	0.3	Ref	1339	0.5	Ref	1141	0.4	Ref
Multiple	91248	21	0.2	0.8 (0.5-1.3)	55	0.6	1.2 (0.9-1.6)	44	0.5	1.1 (0.8-1.5)
Conception Month										
January	214684	66	0.3	1.3 (0.9-1.9)	111	0.5	1.3 (1.0-1.7)	98	0.4	1.2 (0.9-1.6)
February	200962	58	0.3	1.3 (0.9-1.8)	119	0.6	1.5 (1.1-1.9)	108	0.5	1.4 (1.1-1.9)
March	220111	69	0.3	1.4 (1.0-1.9)	134	0.6	1.5 (1.2-2.0)	100	0.4	1.2 (0.9-1.6)
April	212932	66	0.3	1.4 (1.0-1.9)	98	0.5	1.1 (0.9-1.5)	112	0.5	1.4 (1.1-1.8)
May	223165	61	0.3	1.2 (0.8-1.7)	98	0.4	1.1 (0.8-1.4)	83	0.4	1.0 (0.7-1.3)

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		CL			CLP			CP		
	Total Births	**Cases**	**Prev.[a] (/1,000)**	**PR (95% CI)**	**Cases**	**Prev.[a] (/1,000)**	**PR (95% CI)**	**Cases**	**Prev.[a] (/1,000)**	**PR (95% CI)**
June	221264	58	0.3	1.1 (0.8-1.7)	127	0.6	1.4 (1.1-1.9)	106	0.5	1.3 (1.0-1.7)
July	237564	66	0.3	1.2 (0.9-1.7)	113	0.5	1.2 (0.9-1.6)	91	0.4	1.0 (0.8-1.4)
August	238538	58	0.2	1.1 (0.7-1.5)	113	0.5	1.2 (0.9-1.5)	99	0.4	1.1 (0.8-1.5)
September	233870	48	0.2	0.9 (0.6-1.3)	114	0.5	1.2 (0.9-1.6)	96	0.4	1.1 (0.8-1.4)
October	249329	57	0.2	Ref	100	0.4	Ref	94	0.4	Ref
November	234661	74	0.3	1.4 (1.0-1.9)	155	0.7	1.6 (1.3-2.1)	102	0.4	1.1 (0.9-1.5)
December	244384	70	0.3	1.3 (0.9-1.8)	117	0.5	1.2 (0.9-1.6)	105	0.4	1.1 (0.9-1.5)
Site of Maternal Residence										
Arkansas	261703	80	0.3	1.3 (1.0-1.8)	157	0.6	1.3 (1.0-1.6)	131	0.5	1.0 (0.8-1.3)
California	430118	124	0.3	1.2 (0.9-1.6)	249	0.6	1.3 (1.0-1.5)	165	0.4	0.8 (0.6-1.0)
Iowa	273917	100	0.4	1.6 (1.2-2.1)	174	0.6	1.4 (1.1-1.7)	142	0.5	1.1 (0.9-1.4)
Massachusetts	471510	113	0.2	1.0 (0.8-1.4)	176	0.4	0.8 (0.7-1.0)	204	0.4	0.9 (0.7-1.1)
New Jersey	181663	57	0.3	1.3 (1.0-1.9)	94	0.5	1.1 (0.9-1.4)	89	0.5	1.0 (0.8-1.3)
New York	247488	51	0.2	0.9 (0.6-1.2)	106	0.4	0.9 (0.7-1.2)	104	0.4	0.9 (0.7-1.1)
Texas	375157	103	0.3	1.2 (0.9-1.6)	229	0.6	1.3 (1.1-1.6)	139	0.4	0.8 (0.6-1.0)
Georgia/CDC	357754	84	0.2	Ref	165	0.5	Ref	171	0.5	Ref
North Carolina	81890	24	0.3	1.2 (0.8-2.0)	34	0.4	0.9 (0.6-1.3)	32	0.4	0.8 (0.6-1.2)
Utah	50653	15	0.3	1.3 (0.7-2.2)	15	0.3	0.6 (0.4-1.1)	17	0.3	0.7 (0.4-1.2)
Year of Estimated Date of Delivery										
1997	65511	14	0.2	0.8 (0.5-1.5)	28	0.4	0.9 (0.6-1.3)	24	0.4	0.8 (0.5-1.2)
1998	407173	115	0.3	1.1 (0.8-1.4)	202	0.5	1.0 (0.8-1.2)	168	0.4	0.9 (0.7-1.1)
1999	412604	119	0.3	1.1 (0.9-1.5)	227	0.5	1.1 (0.9-1.4)	192	0.5	1.0 (0.8-1.2)
2000	403492	103	0.3	Ref	198	0.5	Ref	188	0.5	Ref
2001	378136	105	0.3	1.1 (0.8-1.4)	204	0.5	1.1 (0.9-1.3)	180	0.5	1.0 (0.8-1.3)
2002	282673	86	0.3	1.2 (0.9-1.6)	157	0.6	1.1 (0.9-1.4)	110	0.4	0.8 (0.7-1.1)
2003	289060	78	0.6	1.1 (0.8-1.4)	171	0.6	1.2 (1.0-1.5)	140	0.5	1.0 (0.8-1.3)
2004	430977	131	0.3	1.2 (0.9-1.5)	212	0.5	1.0 (0.8-1.2)	192	0.4	1.0 (0.8-1.2)

[a]Prevalence was calculated per 1,000 live births.

TABLE III

Other Major Anomalies by Cleft Phenotype, The National Birth Defects Prevention Study, 1997-2004

Associated Major Anomaly[a]	CL (N = 751)		CLP (N = 1,399)		CP (N = 1,194)	
	n	%	n	%	n	%
Neural Tube Defects	6	0.8	13	0.9	14	1.2
Anencephaly	4	0.5	8	0.6	7	0.6
Spina bifida	2	0.3	2	0.1	5	0.4
Encephalocele	1	0.1	3	0.2	3	0.3
Defects of the Central Nervous System	5	0.7	41	2.9	74	6.2
Microcephalus	1	0.1	18	1.3	31	2.6
Hydrocephalus	2	0.3	10	0.7	19	1.6
Dandy-Walker malformation	-	-	3	0.2	6	0.5
Absent corpus callosum	2	0.3	6	0.4	22	1.8
Other defects of brain	2	0.3	9	0.6	24	2.0
Defects of spinal cord	-	-	1	0.1	5	0.4
Defects of the Eye	3	0.4	21	1.5	20	1.7
Anophthalmia/Microphthalmia	1	0.1	12	0.9	15	1.3
Cataract	1	0.1	2	0.1	4	0.3
Glaucoma	-	-	-	-	2	0.2
Other defects of eye	1	0.1	10	0.7	8	0.7
Defects of the Ear	4	0.5	11	0.8	22	1.8
Anotia/microtia	4	0.5	11	0.8	18	1.5
Other ear defects	-	-	-	-	6	0.5
Upper Respiratory System Defects	4	0.5	3	0.2	9	0.8
Choanal atresia	3	0.4	3	0.2	6	0.5
Anomalies of trachea	1	0.1	3	0.2	-	-
Lower Respiratory System Defects	1	0.1	1	0.1	9	0.8
Anomalies of the larynx/bronchus	-	-	-	-	6	0.5
Defects of the lung	1	0.1	3	0.2	1	0.1
Cardiovascular Defects	24	3.2	99	7.1	106	8.9
Conotruncal defects	4	0.5	27	1.9	20	1.7

Associated Major Anomaly[a]	CL (N = 751)		CLP (N = 1,399)		CP (N = 1,194)	
	n	%	n	%	n	%
Single ventricle	-	-	2	0.1	1	0.1
Septal defects	17	2.3	76	5.4	76	6.4
Atrioventricular septal defects	1	0.1	8	0.6	7	0.6
Ebstein malformation	-	-	-	-	2	0.2
Right obstructive heart defects	7	0.9	16	1.1	15	1.3
Left obstructive heart defects	2	0.3	12	0.9	13	1.1
Anomalous pulmonary venous return	-	-	5	0.4	2	0.2
Heterotaxia	-	-	3	0.2	2	0.2
Persistent aortic arch	2	0.3	6	0.4	8	0.7
Other cardiovascular defects	6	0.8	30	2.1	26	2.1
Gastrointestinal Defects	3	0.4	35	2.5	32	2.7
Esophageal atresia/Tracheoesphageal fistula	1	0.1	12	0.9	8	0.7
Intestinal atresia/stenosis	2	0.3	7	0.5	7	0.6
Pyloric stenosis	-	-	5	0.4	7	0.6
Malrotation	-	-	13	0.9	11	0.9
Other gastrointestinal defects	-	-	3	0.2	3	0.3
Defects of the Renal/Urinary System	8	1.1	17	1.2	33	2.8
Renal agenesis	3	0.4	5	0.4	9	0.8
Cystic ~~of~~ kidneys	2	0.3	3	0.2	7	0.6
Congenital hydronephrosis	5	0.7	6	0.4	9	0.8
Ureteral defects	5	0.7	-	-	7	0.6
Other defects of the renal/urinary system	1	0.1	5	0.4	9	0.8
Defects of the Genital System	1	0.1	8	0.6	6	0.5
Hypospadias (2nd or 3rd degree)	-	-	5	0.4	2	0.2
Other genital defects	1	0.1	3	0.2	4	0.3
Limb Defects	12	1.6	48	3.4	80	6.7
Limb deficiencies – Upper	2	0.3	13	0.9	14	1.2
Limb deficiencies – Lower	1	0.1	7	0.5	10	0.8
Clubfoot	5	0.7	17	1.2	35	2.9

Associated Major Anomaly[a]	CL (N = 751)		CLP (N = 1,399)		CP (N = 1,194)	
	n	%	n	%	n	%
Polydactyly – Hand	4	0.5	6	0.4	6	0.5
Polydactyly – Foot	-	-	4	0.3	5	0.4
Syndactyly – Hand	-	-	5	0.4	6	0.5
Syndactyly – Foot	2	0.3	2	0.1	3	0.3
Other defects of the limb	-	-	5	0.4	25	2.1
Musculosketetal Defects	12	1.6	43	3.1	48	4.0
Craniosynostosis	-	-	4	0.3	5	0.4
Gastroschisis	2	0.3	-	-	1	0.1
Omphalocele	1	0.1	5	0.4	2	0.2
Diaphragmatic hernia	2	0.3	4	0.3	2	0.2
Vertebral/rib defects	6	0.8	28	2.0	27	2.3
Congenital hip dislocation	2	0.3	2	0.1	8	0.7
Other musculoskeletal defects	-	-	2	0.1	6	0.5
Defects of Integument	2	0.3	1	0.1	2	0.2
Cystic hygroma	2	0.3	1	0.1	2	0.2

[a] If an infant had more than one defect in the same organ system group, the infant would be counted once for the overall organ system group. Overall organ system groups are not mutually exclusive.

TABLE IV

Reasons for Exclusion of Cleft Patients from CDC and California Sites of the National Birth Defects Prevention Study, 1997-2004

Reason for Exclusion	CL (N = 50)	CLP (N = 122)	CP (N = 157)
Single-gene disorder	3	14	39
Chromosome abnormality			
Trisomy 13	4	37	12
Trisomy 18	6	17	3
Trisomy 21	1	3	10
22q11.2 deletion	0	2	7
Other chromosome abnormalities	6	23	17
Cleft associated with holoprosencephaly	0	2	1
Cleft associated with amniotic band sequence	2	5	1
Cleft associated with another defect[a]	3	6	5
Did not meet inclusion criteria secondary to type of defect[b]			
Microform/pseudocleft lip	8	N/A	N/A
Fused lip/gum	16	N/A	N/A
Submucous cleft palate	N/A	N/A	13
Cleft uvula	N/A	N/A	28
Did not meet inclusion criteria secondary to method of diagnosis	1	9	16
Inappropriate exclusion[c]	0	4	5

[a] Defects include encephalocele, teratoma, and skeletal dysplasia.

[b] 4 additional cases with lateral facial cleft excluded.

[c] Met NBDPS case definition, but were inadvertently excluded from the study.