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Late Detection of Critical Congenital Heart Disease Among US Infants:

Estimation of the Potential Impact of Proposed Universal Screening Using Pulse Oximetry

Cora Peterson, PhD, **Elizabeth Ailes, PhD, MPH**, **Tiffany Riehle-Colarusso, MD, MSE, MPH**, **Matthew E. Oster, MD, MPH**, **Richard S. Olney, MD, MPH**, **Cynthia H. Cassell, PhD**, **David E. Fixler, MD, MSc**, **Suzan L. Carmichael, PhD**, **Gary M. Shaw, DrPH**, and **Suzanne M. Gilboa, PhD, MHS**

Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia (Peterson, Ailes, Riehle-Colarusso, Oster, Olney, Cassell, Gilboa); currently affiliated with National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia (Peterson); Epidemic Intelligence Service, Scientific Education and Professional Development Program Office, Centers for Disease Control and Prevention, Atlanta, Georgia (Ailes); Sibley Heart Center, Children's Healthcare of Atlanta, Emory University, Atlanta, Georgia (Oster); Department of Pediatrics, The University of Texas Southwestern Medical Center, Dallas (Fixler); Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University Medical School, Palo Alto, California (Carmichael, Shaw)

Abstract

IMPORTANCE—Critical congenital heart disease (CCHD) was added to the Recommended Uniform Screening Panel for Newborns in the United States in 2011. Many states have recently adopted or are considering requirements for universal CCHD screening through pulse oximetry in birth hospitals. Limited previous research is directly applicable to the question of how many US infants with CCHD might be identified through screening.

Corresponding Author: Cora Peterson, PhD, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Mailstop F-62, 4770 Buford Hwy, Atlanta, GA 30341 (cora.peterson@cdc.hhs.gov).

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Study concept and design: Peterson, Ailes, Gilboa.
Acquisition of data: Peterson.
Analysis and interpretation of data: All authors.
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Statistical analysis: Ailes, Gilboa.
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OBJECTIVES—To estimate the proportion of US infants with late detection of CCHD (>3 days after birth) based on existing clinical practice and to investigate factors associated with late detection.

DESIGN, SETTING, AND PARTICIPANTS—Descriptive and multivariable analysis. Data were obtained from a multisite population-based study of birth defects in the United States, the National Birth Defects Prevention Study (NBDPS). We included all live-born infants with estimated dates of delivery from January 1, 1998, through December 31, 2007, and nonsyndromic, clinically verified CCHD conditions potentially detectable through screening via pulse oximetry.

MAIN OUTCOMES AND MEASURES—The main outcome measure was the proportion of infants with late detection of CCHD through echocardiography or at autopsy under the assumption that universal screening at birth hospitals might reduce the number of such late diagnoses. Secondary outcome measures included prevalence ratios for associations between selected demographic and clinical factors and late detection of CCHD.

RESULTS—Of 3746 live-born infants with nonsyndromic CCHD, late detection occurred in 1106 (29.5% [95%CI, 28.1%–31.0%]), including 6 (0.2%) (0.1% –0.4%) first receiving a diagnosis at autopsy more than 3 days after birth. Late detection varied by CCHD type from 9 of 120 infants (7.5%[95%CI, 3.5%–13.8%]) with pulmonary atresia to 497 of 801 (62.0% [58.7%–65.4%]) with coarctation of the aorta. In multivariable analysis, late detection varied significantly by CCHD type and study site, and infants with extracardiac defects were significantly less likely to have late detection of CCHD (adjusted prevalence ratio, 0.58 [95% CI, 0.49–0.69]).

CONCLUSIONS AND RELEVANCE—We estimate that 29.5%of live-born infants with nonsyndromic CCHD in the NBDPS received a diagnosis more than 3 days after birth and therefore might have benefited from routine CCHD screening at birth hospitals. The number of infants in whom CCHD was detected through screening likely varies by several factors, including CCHD type. Additional population-based studies of screening in practice are needed.

Congenital heart defects affect approximately 1%of live births, of which 25%are estimated to be critical and require surgery or catheterization within the first year of life.[1] Infants with critical congenital heart defects (also referred to as *critical congenital heart disease* [CCHD]) who are discharged from birth hospitals without a diagnosis are at risk for cardiovascular collapse and death.[1] Newborn screening for CCHD through pulse oximetry can detect some CCHD conditions (eg, those who present with hypoxemia [low blood oxygen saturation] shortly after birth) even in the absence of other physical symptoms and thereby avert late detection.[2] Screening is recommended at birth hospitals within 24 to 48 hours of birth.[3] Pulse oximetry is a noninvasive test that quantifies hypoxemia. A single reading of less than 90% from a neonate's hand or foot or the combination of a 90% to 95%single reading and a difference of more than 3% in the readings for the upper and lower extremities is flagged for follow-up.[3] In recent clinical studies, pulse oximetry has demonstrated high specificity and moderate sensitivity to detect CCHD and a low false-positive rate.[2,4] Critical congenital heart disease was added to the US recommended uniform screening panel for newborns in 2011.[5] Legislation to require screening was recently adopted or is under consideration in most states (http://www.aap.org/stateadvocacy).[6,7]

Previous studies have examined issues related to late CCHD detection (defined for our study as >3 days after birth), although few such studies facilitate direct estimates of the impact that universal screening might have in the United States. For example, several potentially relevant US studies were not population based or lacked sufficient follow-up to identify infants with missed CCHD after discharge from the birth hospital.[8–13] Studies from European countries and elsewhere in the world are illuminating, but not directly applicable to the US clinical context.[14–27] The most relevant US population-based studies of late detection of CCHD published before the federal recommendation for routine screening through pulse oximetry produced widely varied estimates—ranging from 4.3% to 31.3%—of infants with CCHD who received late diagnoses (Table 1).[29–33,35] The substantial variability of those estimates appears to result from differences in case definition, data sources, length of follow-up, study size, and exclusive use of administrative coding to identify CCHD diagnoses. Administrative diagnostic codes may inaccurately classify some heart defects; for example, the severity of aortic or pulmonary stenosis can determine whether such conditions can be detected by screening, although such severity is not distinguished through administrative codes.[36,37] Moreover, those studies did not examine late detection in a manner suited to estimate the potential effect of universal screening; for example, some studies examined only missed diagnoses resulting in infant death[33,35] or did not examine the full range of CCHD conditions that screening might detect.[29–33] At least 2 studies[28,34] have examined the population-based effect of newborn CCHD screening in practice: one was a pilot study at 2 hospitals in New York,[34] and the other was a statewide study of birth hospitals in New Jersey.[28] Both studies reported screening results during a short period and produced very different relative and absolute estimates of late-detected CCHD (25.0% vs 5.9% of newborns with CCHD) (Table 1).

As CCHD screening is more widely adopted, more precise estimation of its impact may be possible by reviewing actual clinical experiences for many years in multiple geographic areas. Until then, retrospective review of infants' CCHD diagnostic experiences remains a relevant way to estimate the potential future effect of universal screening. The purpose of this study was to estimate the proportion of US infants with clinically validated, nonsyndromic, screening-detectable CCHD whose condition was detected late, defined as detection more than 3 days after birth, and to investigate clinical and demographic factors associated with late detection.

Methods

Study Population

The National Birth Defects Prevention Study (NBDPS) is an ongoing, multisite, population-based case-control study conducted in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey [through 2002], New York, North Carolina [beginning 2003], Texas, and Utah [beginning 2003]) to investigate genetic and environmental risk factors for selected major structural birth defects.[38] Population-based ascertainment of infants with birth defects at each study site ranges from entire states (Arkansas, Iowa, New Jersey, and Utah) to selected regions within states (California, Georgia, Massachusetts, New York, North Carolina, and Texas). New York was the only NBDPS site included in this analysis

that relied on a combination of active and passive case ascertainment; all other study sites used active case ascertainment. For our purposes, *active ascertainment* means that trained staff culled multiple medical records to identify and extract pertinent phenotypic information. Infants with recognized or strongly suspected chromosomal abnormalities or single-gene conditions were excluded from the study. The NBDPS reports clinical information abstracted from maternal and infant medical records by birth defects surveillance programs at each study site. Inclusion criteria for congenital heart defects in the NBDPS require that the defects be confirmed by echocardiography, catheterization, surgery, or autopsy findings.[39] The NBDPS gathers additional information on demographic characteristics, exposures (eg, nutritional, behavioral, or occupational) and medication use before and during pregnancy through telephone interviews with the mothers. Interviews are conducted in English or Spanish 6 weeks to 24 months after an infant's estimated date of delivery (EDD). Approximately 63% of mothers of infants with congenital heart defects participated in the telephone interview. The NBDPS was approved by institutional review boards at the Centers for Disease Control and Prevention and all study sites.

In this analysis, we considered all live-born infants with congenital heart defects with an EDD from January 1, 1998, through December 31, 2007, and whose mothers were interviewed for the NBDPS. We excluded all infants born to mothers residing in New Jersey for all years and to mothers residing in Texas with an EDD before June 1998, because those study sites included only a sample of eligible infants with congenital heart defects in the NBDPS. The NBDPS methods for classifying congenital heart defects in infants have been described previously.[39,40] Briefly, classification is based on the primary congenital heart defect by a team of clinicians with expertise in pediatric cardiology and clinical genetics.

For this study, we restricted our analysis to infants with CCHD potentially detectable by screening, defined as hypoplastic left heart syndrome, pulmonary atresia, dextrotransposition of the great arteries, truncus arteriosus, tricuspid atresia, tetralogy of Fallot, total anomalous pulmonary venous return, critical aortic stenosis, coarctation of the aorta, double-outlet right ventricle, Ebstein anomaly, interrupted aortic arch, critical pulmonary stenosis, and single ventricle.[1] The first 7 conditions usually present with hypoxemia and are classified as primary screening targets.[3] Infants with at least 1 screening-detectable CCHD condition were identified through the existing NBDPS heart classification system,[39] with 2 exceptions. First, infants with congenital heart defects classified as multiple complex, other associations, unbalanced atrioventricular septal defects with or without outflow tract obstruction, or laterality defects underwent review by one of us (T.R.-C.) with expertise in pediatric cardiology and the NBDPS heart classification system to determine if 1 or more of the screening-detectable CCHD conditions was present. Second, infants with aortic or pulmonary stenosis were included only when the NBDPS clinical classifiers' comments indicated that the infant underwent valvuloplasty or had critical or severe valve stenosis. Among infants with 1 screening-detectable CCHD, results are presented by individual CCHD type. Infants with more than 1 such condition (eg, coarctation of aorta and double-outlet right ventricle) are reported in a multiple CCHD category.

Identifying Late CCHD Detection

Based on abstracted medical record information, we identified the first date on which infants with CCHD underwent a diagnostic echocardiography (fetal or postnatal) or autopsy. Because CCHD screening is recommended to occur at 24 to 48 hours after birth,[3] we classified CCHD detection as late if the infant did not have abstracted evidence of having received a diagnostic echocardiography prenatally or within 3 days of birth. We conservatively selected 3 days rather than 2 because the NBDPS does not capture time of birth; therefore, a cutoff of 2 days might erroneously identify infants as having late CCHD detection when a diagnosis was made within 48 hours. Every infant who received a first diagnosis at autopsy could reasonably be considered to have late detection of CCHD. However, we excluded infants with a diagnosis at autopsy within 3 days of birth because we aimed to quantify the proportion of infants with CCHD who might benefit from proposed universal screening, and such infants might not have the chance to undergo screening. We also excluded infants who did not have a recorded echocardiography. Such infants were assumed to have incomplete records in the NBDPS because interventions (ie, cardiac catheterization or surgery) are usually preceded by or accompanied by imaging studies. We restricted the analysis to infants with CCHD diagnosis by echocardiography performed within 1 year of age.[1]

Statistical Analysis

We first assessed the timing of infants' CCHD diagnosis (prenatal, postnatal, or at autopsy) through descriptive statistics by calculating frequencies and their corresponding 95%Wald CIs. We used exact 95%CIs for cell counts less than 10. We then estimated crude and adjusted prevalence ratios (PRs) and corresponding 95% CIs for late detection based on selected infant and maternal demographic and clinical characteristics in Poisson regression models with robust sandwich error variance.[41,42]We assessed the following characteristics from information abstracted from birth defects surveillance data: NBDPS study site, the presence of extracardiac defects (ie, major defects in organ systems outside of the heart),[39] CCHD type, gestational age at delivery, and EDD year. We assessed the following characteristics from information reported during the NBDPS maternal interview: first-degree family history of congenital heart defects, plurality, and maternal characteristics, including race/ethnicity, age at delivery, education, diabetes mellitus before or during the index pregnancy, prepregnancy body mass index, hypertension before or during the pregnancy, fertility treatments, previous pregnancy losses, and trimester of the first prenatal care visit. The analysis was conducted using commercially available statistical software (SAS, version 9.2; SAS Institute, Inc).

Results

Of 9441 infants with nonsyndromic congenital heart defects and a 1998–2007 EDD whose mothers participated in an NBDPS interview, 3746 were included in the analysis (Figure). Of these, 1106 (29.5% [95% CI, 28.1%–31.0%]) underwent diagnosis through echocardiography more than 3days after birth (Table 2). For 6 infants (0.2% [95% CI, 0.1%–0.4%]), CCHD diagnosis occurred at autopsy more than 3 days after birth (Table 2). Late detection by CCHD type ranged from 9 of 120 infants (7.5%[95%CI, 3.5%–

13.8%])with pulmonary atresia to 497 of 801 (62.0%[58.7%–65.4%])with coarctation of the aorta (Table 2). The frequency of late detection varied within CCHD types by the presence or absence of extracardiac defects and by NBDPS study site (Supplement [eFigures 1 and 2]). For 542 infants (14.5% [95% CI, 13.3%–15.6%]), the first echocardiogram documented in the abstracted medical record was prenatal. Among infants with late-detected CCHD diagnosed through echocardiography (n = 1100), the median time from birth to diagnosis was 14 (range, 4–363; interquartile range [IQR], 7–48) days (Table 2). Among the 6 infants who received the initial diagnosis at autopsy more than 3 days after birth (n = 6), the median time from birth to diagnosis was 5 (range, 4–21; IQR, 4–11) days (data not shown).

When we controlled for all demographic and clinical factors under consideration, the prevalence of late detection among infants with CCHD varied significantly by the presence of extracardiac defects, CCHD type, and NBDPS study site (Table 3). The estimated adjusted prevalence of late detection among infants with extracardiac defects was 42% less (adjusted PR, 0.58 [95% CI, 0.49–0.69]) than the adjusted prevalence in infants without extracardiac defects (Table 3). The estimated adjusted prevalence of late detection among infants with Ebstein anomaly, single ventricle, critical pulmonary stenosis, interrupted aortic arch, tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus, total anomalous pulmonary venous return, and coarctation of the aorta were each significantly greater than the adjusted prevalence among infants with hypoplastic left heart syndrome (the reference group). Late detection varied significantly by NBDPS study site, with a 2-fold difference between the sites with the lowest and highest adjusted prevalence of late detection (adjusted PR, 2.09 [95% CI, 1.66–2.63]) (Table 3).

Discussion

Based on data from the NBDPS, we estimated that the diagnosis of nonsyndromic CCHD occurred more than 3 days after birth in 29.5%of infants, including fewer than 1%with the initial diagnosis at autopsy. These infants, therefore, might have benefited from universal screening through pulse oximetry at their birth hospitals. Infants with extracardiac defects were significantly less likely to have late detection, and late detection varied by CCHD type and NBDPS study site.

Our study focused explicitly on the potential effect of new US recommendations for CCHD screening using multisite data and examined the diagnostic experience of infants with CCHD during the entire first year of life. Our estimate is similar to that of a retrospective study at an NBDPS contributing site— metropolitan Atlanta—that estimated that 31.3%of infants with CCHD did not receive a diagnosis on their day of birth.[31] Other retrospective US studies with substantially lower estimated proportions of infants with late detection of CCHD (ie, 4%–7%)[32,35] examined fewer CCHD types than our study or identified late detection of CCHD only through the occurrence of death.[33,35] However, estimates from most previous studies of late CCHD detection[28–30,32–35] (Table 1) appear to have included infants with genetic disorders, whereas our study excluded such infants. Most previous studies[29,30,32,35] used exclusively administrative coding to identify CCHD diagnoses, which might inaccurately classify heart defects or fail to capture whether a defect such as aortic stenosis or pulmonary stenosis is critical.[36,37] Previous studies of late CCHD detection also

used different data sources—such as hospital admission records with or without accompanying statewide death records— to identify infants with late detection of CCHD. One previous study[30] ascertained infants with late detection of CCHD less than 1 month after birth. Finally, previous studies were limited to 2 hospitals,[34] a single metropolitan area,[31,35] or a single state.[28–30,32,33]

In our study, the prevalence of late detection varied widely (from 7.5% to 62.0%) by CCHD type. Evidence suggests that the sensitivity of CCHD screening through pulse oximetry also may vary substantially by CCHD type—a proxy for the presence of hypoxemia. A recent meta-analysis[2] reported that pulse oximetry conducted at least 24 hours after birth was 78% sensitive to detect CCHD overall. However, a review of 13 screening studies[43] (with 258 809 infants undergoing screening, of whom 256 were ultimately diagnosed as having CCHD) from 1998 through 2009 reported sensitivities ranging from 36% (95% CI, 24%–50%) for coarctation of the aorta and interrupted aortic arch (18 of 50 infants) to 100% (95% CI, 44%–100%) for single ventricle (6 of 6 infants), double-outlet right ventricle (5 of 5 infants), and pulmonary atresia with intact septum (3 of 3 infants). Screening-detectable CCHD constitutes a heterogeneous group of rare congenital heart defects, and the numbers of infants included in these CCHD defect–specific estimates are very small. The high rate of late detection among infants with coarctation of the aorta (62.0%) in our study influenced our overall estimate of 29.5% late detection; excluding these infants would result in an overall estimate of late detection in 609 of 2945 (20.7% [95% CI, 19.2%–22.2%]). Nonhypoxemic cases of coarctation of the aorta (ie, not detectable through screening) likely contributed to our estimated prevalence of late detection for that condition. Unfortunately, we were unable to ascertain lesion severity.

Infants with extracardiac defects were less likely to have late detection of CCHD in our study. Infants with birth defects affecting multiple organ systems may receive additional medical attention prenatally or at birth, which might explain why late detection was significantly lower among such infants. The proportion of infants in our study with nonsyndromic extracardiac defects (17.0% [95% CI, 15.8%- 18.2%]) was similar to those of other population-based studies of infants and children with congenital heart defects.[44,45] However, because the NBDPS excludes infants with genetic syndromes, our study might have estimated a higher proportion of late detection than actually exists in the population. Our results also indicated that late CCHD detection varied significantly among the 9 NBDPS study sites included in this analysis. This variation may reflect, in part, nonuniformity in neonatal clinical practice, which cannot be addressed using existing birth defects surveillance data in the NBDPS. In addition, the NBDPS sites draw from different populations in terms of socioeconomic status, urbanicity, and geographic region; thus, inference about the underlying meaning of the observed study site variability would require further investigation.

We found no significant temporal trend in terms of increasing or decreasing prevalence of late CCHD detection during the study period (Table 2). Recent studies[46–49] have reported inconsistent findings about whether race/ethnicity is associated with outcomes such as mortality and hospital readmission among infants with congenital heart defects, although no significant racial/ethnic associations were observed in this analysis. We found no significant

association between the timing of the first prenatal care visit and timely CCHD detection; however, this variable is a limited indicator of the experience of prenatal care.

This study has a number of limitations. The NBDPS does not explicitly seek information on the initial diagnosis of congenital heart defects, but instead a diagnosis by specific means (echocardiography, autopsy, catheterization, or surgery). Therefore, we may have overestimated the proportion of infants with late CCHD detection owing to missing information on initial diagnoses. However, echocardiography is recommended to diagnose CCHD, even if an infant receives a definitive diagnosis through other means.[3,50] Missing or erroneous examination information might vary by NBDPS site because ascertainment of follow-up records (ie, outpatient echocardiography) is not standardized. Another limitation is that we restricted our analysis to infants in the NBDPS whose mothers were interviewed. Because infants of noninterviewed mothers did not undergo classification by NBDPS clinicians, we were unable to compare the 2 groups. A related limitation is that many of the factors we assessed were based on mothers' self-reported demographic and clinical information (ie, timing of entry into prenatal care, diabetes mellitus status, and prepregnancy body mass index).

Our study has 3 notable strengths that distinguish it from previous US studies. First, we used data compiled from multiple population-based birth defects surveillance programs that included infants with clinically validated CCHD diagnoses.[51] Second, because we used abstracted medical records to identify and classify infants according to CCHD type, we likely have achieved greater clinical accuracy than previous studies that relied exclusively on administrative data to classify CCHD diagnoses. Third, we used clinical definitions of CCHD and timely detection that are directly pertinent to new US federal recommendations for universal newborn screening for CCHD through pulse oximetry.

Conclusions

We estimate that 29.5% of live-born infants with nonsyndromic CCHD in the NBDPS received the diagnosis more than 3 days after birth. The proportions of infants with late CCHD detection varied substantially by CCHD type, from 7.5% (pulmonary atresia) to 62.0% (coarctation of the aorta). These results suggest that many infants with CCHD might benefit from screening through pulse oximetry before birth hospital discharge. Whether such infants are detected through screening is likely to vary by a number of factors, including CCHD type and the presence of extracardiac defects. Additional population-based studies of universal screening in practice are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Mahle WT, Newburger JW, Matherne GP, et al. American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Interdisciplinary Council on Quality of Care and Outcomes Research; American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, and Committee on Fetus and Newborn. Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the American Heart Association and American Academy of Pediatrics. Circulation. 2009; 120(5):447–458. [PubMed: 19581492]
2. Thangaratinam S, Daniels J, Ewer AK, Zamora J, Khan KS. Accuracy of pulse oximetry in screening for congenital heart disease in asymptomatic newborns: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2007; 92(3):F176–F180. [PubMed: 17344253]
3. Kemper AR, Mahle WT, Martin GR, et al. Strategies for implementing screening for critical congenital heart disease. Pediatrics. 2011; 128(5):e1259–e1267. [PubMed: 21987707]
4. Ewer AK. Review of pulse oximetry screening for critical congenital heart defects in newborn infants. Curr Opin Cardiol. 2013; 28(2):92–96. [PubMed: 23381095]
5. [Accessed November 1, 2011] Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. HHS Secretary adopts recommendation to add critical congenital heart disease to the recommended uniform screening panel. http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/index.html.Published 2011
6. Centers for Disease Control and Prevention. Rapid implementation of pulse oximetry newborn screening to detect critical congenital heart defects: New Jersey, 2011. MMWR Morb Mortal Wkly Rep. 2013; 62(15):292–294. [PubMed: 23594686]
7. Centers for Disease Control and Prevention. Assessment of current practices and feasibility of routine screening for critical congenital heart defects: Georgia, 2012. MMWR Morb Mortal Wkly Rep. 2013; 62(15):288–291. [PubMed: 23594685]
8. Hoke TR, Donohue PK, Bawa PK, et al. Oxygen saturation as a screening test for critical congenital heart disease: a preliminary study. Pediatr Cardiol. 2002; 23(4):403–409. [PubMed: 12170356]
9. Reich JD, Miller S, Brogdon B, et al. The use of pulse oximetry to detect congenital heart disease. J Pediatr. 2003; 142(3):268–272. [PubMed: 12640374]
10. Reich JD, Connolly B, Bradley G, et al. The reliability of a single pulse oximetry reading as a screening test for congenital heart disease in otherwise asymptomatic newborn infants. Pediatr Cardiol. 2008; 29(5):885–889. [PubMed: 18347842]
11. Schultz AH, Localio AR, Clark BJ, Ravishankar C, Videon N, Kimmel SE. Epidemiologic features of the presentation of critical congenital heart disease: implications for screening. Pediatrics. 2008; 121(4):751–757. [PubMed: 18381540]
12. Bradshaw EA, Cuzzi S, Kiernan SC, Nagel N, Becker JA, Martin GR. Feasibility of implementing pulse oximetry screening for congenital heart disease in a community hospital. J Perinatol. 2012; 32(9):710–715. [PubMed: 22282131]
13. Walsh W. Evaluation of pulse oximetry screening in Middle Tennessee: cases for consideration before universal screening. J Perinatol. 2011; 31(2):125–129. [PubMed: 20508595]
14. Abu-Harb M, Hey E, Wren C. Death in infancy from unrecognised congenital heart disease. Arch Dis Child. 1994; 71(1):3–7. [PubMed: 8067789]
15. Wren C, Richmond S, Donaldson L. Presentation of congenital heart disease in infancy: implications for routine examination. Arch Dis Child Fetal Neonatal Ed. 1999; 80(1):F49–F53. [PubMed: 10325813]

16. Bakr AF, Habib HS. Combining pulse oximetry and clinical examination in screening for congenital heart disease. Pediatr Cardiol. 2005; 26(6):832–835. [PubMed: 16088415]
17. Rosati E, Chitano G, Dipaola L, De Felice C, Latini G. Indications and limitations for a neonatal pulse oximetry screening of critical congenital heart disease. J Perinat Med. 2005; 33(5):455–457. [PubMed: 16238542]
18. Arlettaz R, Bauschatz AS, Mönkhoff M, Essers B, Bauersfeld U. The contribution of pulse oximetry to the early detection of congenital heart disease in newborns. Eur J Pediatr. 2006; 165(2):94–98. [PubMed: 16211399]
19. Brown KL, Ridout DA, Hoskote A, Verhulst L, Ricci M, Bull C. Delayed diagnosis of congenital heart disease worsens preoperative condition and outcome of surgery in neonates. Heart. 2006; 92(9):1298–1302. [PubMed: 16449514]
20. Mellander M, Sunnegårdh J. Failure to diagnose critical heart malformations in newborns before discharge: an increasing problem? Acta Paediatr. 2006; 95(4):407–413. [PubMed: 16720486]
21. Ruangritnamchai C, Bunjapamai W, Pongpanich B. Pulse oximetry screening for clinically unrecognized critical congenital heart disease in the newborns. Images Paediatr Cardiol. 2007; 9(1):10–15. [PubMed: 22368668]
22. Meberg A, Brügmann-Pieper S, Due R Jr, et al. First day of life pulse oximetry screening to detect congenital heart defects. J Pediatr. 2008; 152(6):761–765. [PubMed: 18492511]
23. Wren C, Reinhardt Z, Khawaja K. Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations. Arch Dis Child Fetal Neonatal Ed. 2008; 93(1):F33–F35. [PubMed: 17556383]
24. de-Wahl Granelli A, Wennergren M, Sandberg K, et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. BMJ. 2009; 338:a3037. [PubMed: 19131383]
25. Meberg A, Andreassen A, Brunvand L, et al. Pulse oximetry screening as a complementary strategy to detect critical congenital heart defects. Acta Paediatr. 2009; 98(4):682–686. [PubMed: 19154526]
26. Ewer AK, Middleton LJ, Furmston AT, et al. PulseOx Study Group. Pulse oximetry screening for congenital heart defects in newborn infants (PulseOx): a test accuracy study. Lancet. 2011; 378(9793):785–794. [PubMed: 21820732]
27. Turska Kmieć A, Borszewska Kornacka MK, Błaż W, Kawalec W, Zuk M. Early screening for critical congenital heart defects in asymptomatic newborns in Mazovia province: experience of the POLKARD pulse oximetry programme 2006–2008 in Poland. Kardiol Pol. 2012; 70(4):370–376. [PubMed: 22528711]
28. Garg LF, Van Naarden Braun K, Knapp MM, et al. Results from the New Jersey Statewide critical congenital heart defects screening program. Pediatrics. 2013; 132(2):e314–e323. [PubMed: 23858425]
29. Peterson C, Dawson A, Grosse SD, et al. Hospitalizations, costs, and mortality among infants with critical congenital heart disease: how important is timely detection? Birth Defects Res A Clin Mol Teratol. 2013; 97(10):664–672. [PubMed: 24000201]
30. Ng B, Hokanson J. Missed congenital heart disease in neonates. Congenit Heart Dis. 2010; 5(3): 292–296. [PubMed: 20576049]
31. Oster ME, Lee KA, Honein MA, Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics. 2013; 131(5):e1502–e1508. [PubMed: 23610203]
32. Aamir T, Kruse L, Ezeakudo O. Delayed diagnosis of critical congenital cardiovascular malformations (CCVM) and pulse oximetry screening of newborns. Acta Paediatr. 2007; 96(8): 1146–1149. [PubMed: 17590190]
33. Chang RK, Gurvitz M, Rodriguez S. Missed diagnosis of critical congenital heart disease. Arch Pediatr Adolesc Med. 2008; 162(10):969–974. [PubMed: 18838650]
34. Koppel RI, Druschel CM, Carter T, et al. Effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns. Pediatrics. 2003; 111(3):451–455. [PubMed: 12612220]
35. Kuehl KS, Loffredo CA, Ferencz C. Failure to diagnose congenital heart disease in infancy. Pediatrics. 1999; 103(4, pt 1):743–747. [PubMed: 10103296]

36. Frohnert BK, Lussky RC, Alms MA, Mendelsohn NJ, Symonik DM, Falken MC. Validity of hospital discharge data for identifying infants with cardiac defects. J Perinatol. 2005; 25(11):737–742. [PubMed: 16163368]
37. Strickland MJ, Riehle-Colarusso TJ, Jacobs JP, et al. The importance of nomenclature for congenital cardiac disease: implications for research and evaluation. Cardiol Young. 2008; 18(suppl 2):92–100. [PubMed: 19063779]
38. Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. Public Health Rep. 2001; 116(suppl 1):32–40. [PubMed: 11889273]
39. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A. National Birth Defects Prevention Study. Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res A Clin Mol Teratol. 2007; 79(10):714–727. [PubMed: 17729292]
40. Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. National Birth Defects Prevention Study. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol. 2003; 67(3):193–201. [PubMed: 12797461]
41. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004; 159(7):702–706. [PubMed: 15033648]
42. Lee J, Tan CS, Chia KS. A practical guide for multivariate analysis of dichotomous outcomes. Ann Acad Med Singapore. 2009; 38(8):714–719. [PubMed: 19736577]
43. Prudhoe S, Abu-Harb M, Richmond S, Wren C. Neonatal screening for critical cardiovascular anomalies using pulse oximetry. Arch Dis Child Fetal Neonatal Ed. 2013; 98(4):F346–F350. [PubMed: 23341250]
44. Lurie IW, Kappetein AP, Loffredo CA, Ferencz C. Non-cardiac malformations in individuals with outflow tract defects of the heart: the Baltimore-Washington Infant Study (1981–1989). Am J Med Genet. 1995; 59(1):76–84. [PubMed: 8849016]
45. Oyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PK, Melbye M. National time trends in congenital heart defects, Denmark, 1977–2005. Am Heart J. 2009; 157(3):467.e1–473.e1. [PubMed: 19249416]
46. Ingaramo OA, Khemani RG, Markovitz BP, Epstein D. Effect of race on the timing of the Glenn and Fontan procedures for single-ventricle congenital heart disease. Pediatr Crit Care Med. 2012; 13(2):174–177. [PubMed: 21666532]
47. Nembhard WN, Salemi JL, Ethen MK, Fixler DE, Dimaggio A, Canfield MA. Racial/ethnic disparities in risk of early childhood mortality among children with congenital heart defects. Pediatrics. 2011; 127(5):e1128–e1138. [PubMed: 21502234]
48. Kogon B, Jain A, Oster M, Woodall K, Kanter K, Kirshbom P. Risk factors associated with readmission after pediatric cardiothoracic surgery. Ann Thorac Surg. 2012; 94(3):865–873. [PubMed: 22682942]
49. Fixler DE, Nembhard WN, Xu P, Ethen MK, Canfield MA. Effect of acculturation and distance from cardiac center on congenital heart disease mortality. Pediatrics. 2012; 129(6):1118–1124. [PubMed: 22566422]
50. Mahle WT, Martin GR, Beekman RH III, Morrow WR. Section on Cardiology and Cardiac Surgery Executive Committee. Endorsement of Health and Human Services recommendation for pulse oximetry screening for critical congenital heart disease. Pediatrics. 2012; 129(1):190–192. [PubMed: 22201143]
51. Olney RS, Botto L. Newborn screening for critical congenital heart disease: essential public health roles for birth defects monitoring programs. Birth Defects Res A Clin Mol Teratol. 2012; 94(12): 965–969. [PubMed: 23184496]

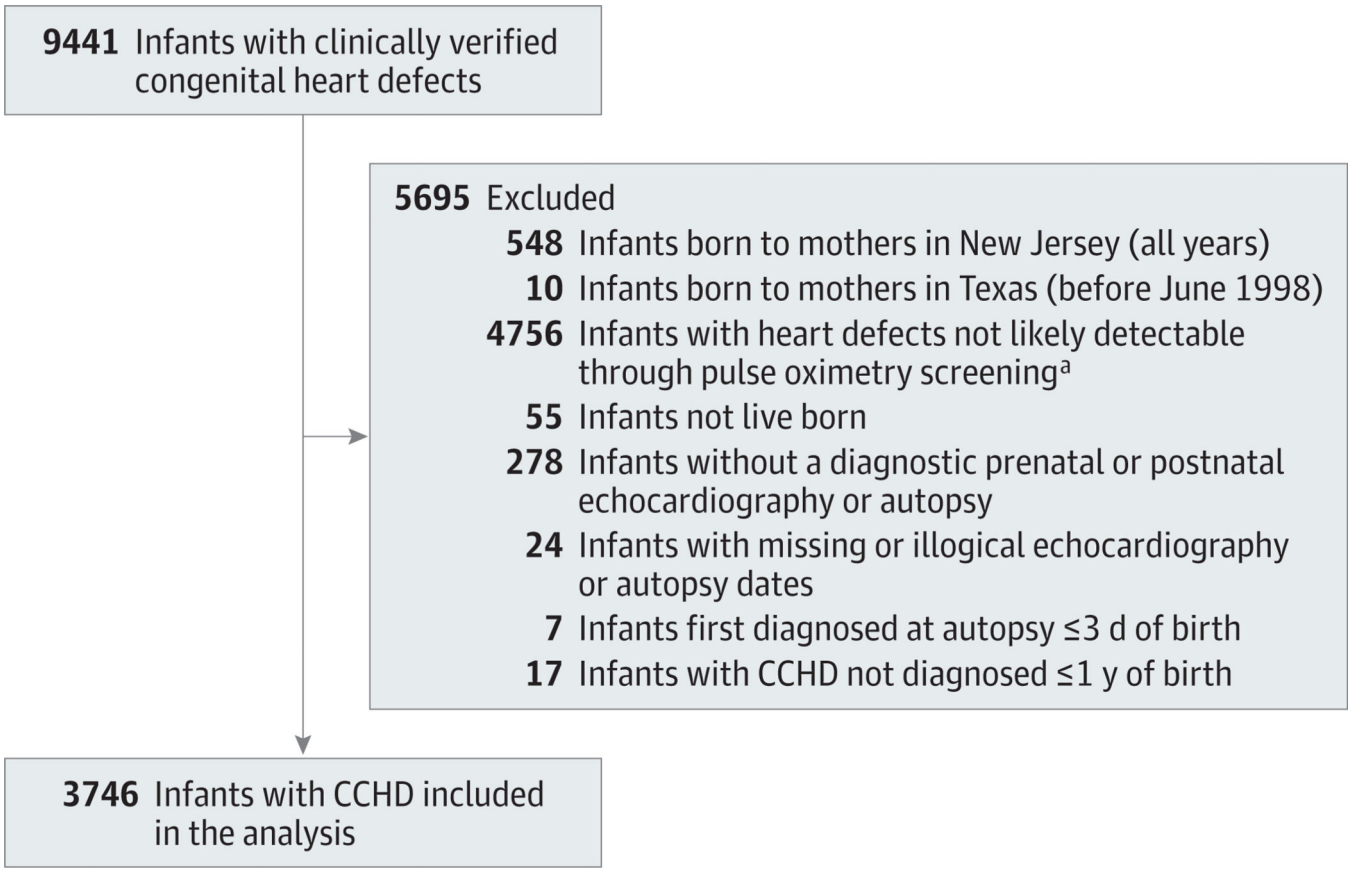

Figure.

Derivation of Study Sample of Infants With Critical Congenital Heart Disease (CCHD) in the National Birth Defects Prevention Study, 1998–2007

[a]Hypoxemic structural heart defects potentially detectable through pulse oximetry screening at birth hospitals include critical aortic stenosis, coarctation of the aorta, double-outlet right ventricle, dextrotransposition of the great arteries, Ebstein anomaly, hypoplastic left heart syndrome, pulmonary atresia, interrupted aortic arch, critical pulmonary stenosis, single ventricle, truncus arteriosus, total anomalous pulmonary venous return, tetralogy of Fallot, and tricuspid atresia.

Table 1

Selected Previous Population-Based Estimates of Late Detection of CCHD Among US Infants

Source	Study Period	Cohort, No. of Patients	No. of Infants With CCHD	Definition of Late Detection	Infants With Late Detection, No. (%)	Data Sources and Limitations
Garg et al,[28] 2013	2011	72 694	51	True positive CCHD screening results in newborns with unsuspected CCHD	3 (5.9)	Data from New Jersey statewide POX screening program in birth hospitals; Dx based on clinical case review; postnatal FU period not defined, although <9 mo; late CCHD detection defined as detected through screening; false-negative results NR
Peterson et al,[29] 2013	1998–2007	2 128 236	3603	Dx after birth hospital discharge	825 (22.9)	Data from Florida Birth Defects Registry plus statewide inpatient and death records; Dx based on *ICD-9-CM* codes; 1-y postnatal case ascertainment; not all screening-detectable CCHD examined[a]
Ng and Hokanson,[30] 2010	2002–2006	345 572	NR	Dx after birth hospital discharge	14 (NC)	Data from Wisconsin statewide hospital and death records; Dx based on *ICD-9-CM* codes; 2-wk postnatal case ascertainment; not all screening-detectable CCHD examined[a]
Oster et al,[31] 2013	1979–2005	1 056 541	1295[b]	Dx after day of birth	405 (31.3)	Data from Metropolitan Atlanta Congenital Defects Program (including statewide death records); Dx based on *ICD-9-CM* codes; case ascertainment as long as6yafter birth; not all screening-detectable CCHD examined[a]; late detection not aligned with current screening recommendations[c]
Aamir et al,[32] 2007	1999–2004	670 245	696	Dx after birth hospital discharge	47 (6.8)	Data from New Jersey birth certificates and statewide hospital records; Dx based on *ICD-9-CM* codes; clinical case review for late detection; 1-y postnatal case ascertainment; not all screening-detectable CCHD examined[a]
Chang et al,[33] 2008	1989–2004	8 869 336[d]	NR	Autopsy-confirmed infant death from CCHD with no heart surgery performed	152 (NC)	Data from California statewide death records; Dx based on *ICD-9-CM* codes; 1-y postnatal case ascertainment; not all screening-detect-able CCHD examined[a]; definition of late detection not aligned with current screening recommendations[c]
Koppel et al,[34] 2003	1998–1999	11 296	20	True-positive or false-negative CCHD screening results in asymptomatic newborns	5 (25.0)	Data from pilot POX screening program in 2 New York state hospitals, New York State Congenital Malformations Registry, and statewide hospital and death records; Dx based on clinical case review; 2-y postnatal case ascertainment
Kuehl et al,[35] 1999	1981–1989	906 626	969	Dx after infant death	42 (4.3)	Data from the Baltimore-Washington Infant Study and area death records; Dx based on clinical case review; 1-y postnatal case ascertainment; definition of late detection not aligned with current screening recommendations[c]

Abbreviations: CCHD, critical congenital heart disease; Dx, diagnosis; FU, follow-up; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; NC, not calculable; NR, not reported; POX, pulse oximetry.

[a] Screening-detectable CCHD conditions include hypoplastic left heart syndrome, pulmonary atresia, dextrotransposition of the great arteries, truncus arteriosus, tricuspid atresia, tetralogy of Fallot, total anomalous pulmonary venous return, critical aortic stenosis, coarctation of the aorta, double-outlet right ventricle, Ebstein anomaly, interrupted aortic arch, critical pulmonary stenosis, and single ventricle.[1]

[b] Estimate excluded infants with noncardiac anomalies.

[c] Screening is recommended to occur at birth hospitals within 24 to 48 hours of birth.[3]

[d] Cohort size reported by California Department of Health for study years (http://www.cdph.ca.gov/data/statistics/Pages/default.aspx).

Table 2

Timing of CCHD Detection via Echocardiography or Autopsy Among 3746 Infants in the National Birth Defects Prevention Study, 1998–2007

	No. of Patients						No. of Patients						
			Day				Day						
	All	Before Birth	1	2	3	Timely Detection, No. (%) [95% CI][a]	4	5	6	≥7	Dx at Autopsy (>Day 3)	Total Late Detection, No. (%) [95% CI][a]	EKG Dx in Late Detection, Time After Birth, Median (Range), d[b]
Single CCHD													
Pulmonary atresia	120	25	52	28	6	111 (92.5) [87.8–97.2]	1	1	0	7	0	9 (7.5) [3.5–13.8][c]	8 (4–205)
Tricuspid atresia	90	23	37	15	4	79 (87.8) [81.0–94.5]	1	1	1	8	0	11 (12.2) [5.5–19.0]	18 (4–95)
Hypoplastic left heart syndrome	427	113	143	62	53	371 (86.9) [83.7–90.1]	16	6	9	23	2	56 (13.1) [9.9–16.3]	6 (4–131)
Dextrotransposition of the great arteries	650	84	282	159	37	562 (86.5) [83.8–89.1]	9	5	3	70	1	88 (13.5) [10.9–16.2]	13 (4–205)
Aortic stenosis, critical	20	3	7	4	2	16 (80.0) [62.5–97.5]	0	1	0	3	0	4 (20.0) [5.7–43.7][c]	9 (5–61)
Ebstein anomaly	90	11	40	18	2	71 (78.9) [70.5–87.3]	6	0	2	11	0	19 (21.1) [12.7–29.5]	7 (4–129)
Single ventricle	127	37	35	21	6	99 (78.0) [70.7–85.2]	5	2	4	17	0	28 (22.0) [14.8–29.3]	10 (4–182)
Pulmonary stenosis, critical	101	8	29	30	11	78 (77.2) [69.1–85.4]	4	4	0	15	0	23 (22.8) [14.6–31.0]	10 (4–215)
Interrupted aortic arch	43	5	5	12	9	31 (72.1) [58.7–85.5]	2	0	0	10	0	12 (27.9) [14.5–41.3]	10 (4–93)
Tetralogy of Fallot	733	94	178	164	93	529 (72.2) [68.9–75.4]	33	10	10	151	0	204 (27.8) [24.6–31.1]	23 (4–361)
Double-outlet right ventricle	94	14	27	19	5	65 (69.1) [59.8–78.5]	3	2	1	23	0	29 (30.9) [21.5–40.2]	17 (4–144)
Truncus arteriosus	68	11	19	9	8	47 (69.1) [58.1–80.1]	3	2	0	15	1	21 (30.9) [19.9–41.9]	14 (4–89)
Total anomalous pulmonary venous return	190	8	48	44	12	112 (58.9) [52.0–65.9]	4	3	2	69	0	78 (41.1) [34.1–48.1]	29 (4–330)
Coarctation of the aorta	801	61	80	90	73	304 (38.0) [34.6–41.3]	42	26	27	400	2	497 (62.0) [58.7–65.4]	15 (4–363)
Multiple CCHD[d]	192	45	77	32	11	165 (85.9) [81.0–90.9]	7	3	3	14	0	27 (14.1) [9.2–19.0]	9 (4–120)
Total	**3746**	**542**	**1059**	**707**	**332**	**2640** (70.5) [69.0–71.9]	**136**	**66**	**62**	**836**	**6**	**1106** (29.5) [28.1–31.0]	14 (4–363)

Abbreviations: CCHD, critical congenital heart disease; Dx, diagnosis; EKG, echocardiography.

[a] Late detection defined as a Dx more than 3 days after birth via echocardiography or autopsy. Percentages have been rounded and might not total 100.

[b] Total includes 1100 infants, excluding 6 who received a first Dx at autopsy (median number of days from birth to autopsy, 5; range: 4–21).

[c] Indicates exact 95%CI.

[d] Indicates more than 1 screening-detectable CCHD.

Table 3

Analysis of Factors Associated With Late Detection of CCHD Among 3746 Infants in the National Birth Defects Prevention Study, 1998–2007[a]

	No. (%) of Infants		PR (95% CI)	
Characteristic	**Total**	**Late Detection[b]**	**Crude Analysis**	**Adjusted Analysis**
Extracardiac defects[c]				
No	3110	980 (31.5)	1 [Reference]	1 [Reference]
Yes	636	126 (19.8)	**0.63 (0.53–0.74)**	**0.58(0.49–0.69)**
CCHD type				
Single CCHD				
Pulmonary atresia	120	9 (7.5)	0.57 (0.29–1.12)	0.73 (0.37–1.43)
Tricuspid atresia	90	11 (12.2)	0.93 (0.51–1.71)	1.05 (0.56–1.97)
Hypoplastic left heart syndrome	427	56 (13.1)	1 [Reference]	1 [Reference]
Dextrotransposition of the great arteries	650	88 (13.5)	1.03 (0.76–1.41)	1.21 (0.87–1.69)
Aortic stenosis, critical	20	4 (20.0)	1.53 (0.61–3.79)	1.64 (0.46–5.86)
Ebstein anomaly	90	19 (21.1)	**1.61 (1.01–2.57)**	**1.72(1.02–2.88)**
Single ventricle	127	28 (22.0)	**1.68 (1.12–2.53)**	**1.92(1.26–2.95)**
Pulmonary stenosis, critical	101	23 (22.8)	**1.74 (1.12–2.68)**	**1.94(1.23–3.04)**
Interrupted aortic arch	43	12 (27.9)	**2.13 (1.24–3.65)**	1.86 (0.98–3.52)
Tetralogy of Fallot	733	204 (27.8)	**2.12 (1.62–2.78)**	**2.42(1.81–3.24)**
Double-outlet right ventricle	94	29 (30.9)	**2.35 (1.59–3.47)**	**2.90(1.90–4.43)**
Truncus arteriosus	68	21 (30.9)	**2.35 (1.53–3.62)**	**2.60(1.64–4.12)**
Total anomalous pulmonary venous return	190	78 (41.1)	**3.13 (2.32–4.22)**	**3.38(2.44–4.68)**
Coarctation of the aorta	801	497 (62.0)	**4.73 (3.68–6.08)**	**5.26(4.02–6.89)**
Multiple CCHD[d]	192	27 (14.1)	1.07 (0.70–1.64)	1.40 (0.90–2.17)
Estimated year of delivery				
1998	261	81 (31.0)	1 [Reference]	1 [Reference]
1999	357	105 (29.4)	0.95 (0.74–1.21)	0.95 (0.75–1.2)
2000	351	121 (34.5)	1.11 (0.88–1.40)	1.07 (0.86–1.34)
2001	362	109 (30.1)	0.97 (0.76–1.23)	1.01 (0.81–1.27)
2002	330	96 (29.1)	0.94 (0.73–1.20)	0.95 (0.75–1.20)
2003	352	112 (31.8)	1.03 (0.81–1.30)	0.96 (0.76–1.22)
2004	463	131 (28.3)	0.91 (0.72–1.15)	0.88 (0.70–1.10)
2005	419	117 (27.9)	0.90 (0.71–1.14)	0.88 (0.70–1.11)
2006	444	108 (24.3)	**0.78 (0.61–1.00)**	**0.71(0.55–0.91)**
2007	407	126 (31.0)	1.00 (0.79–1.26)	0.86 (0.68–1.09)
Family history of congenital heart defects				
No	3613	1072 (29.7)	1 [Reference]	1 [Reference]
Yes	133	34 (25.6)	0.86 (0.64–1.16)	0.87 (0.65–1.15)

Characteristic	No. (%) of Infants		PR (95% CI)	
	Total	Late Detection[b]	Crude Analysis	Adjusted Analysis
Gestational age, wk				
<32 (Very preterm)	138	51 (37.0)	**1.26 (1.01–1.58)**	1.20 (0.96–1.50)
32–36 (Preterm)	557	151 (27.1)	0.93 (0.80–1.07)	1.04 (0.89–1.22)
37–45 (Full term)	3020	885 (29.3)	1 [Reference]	1 [Reference]
Unknown/missing	31	19 (61.3)	NC	NC
Plurality				
Singleton	3509	1029 (29.3)	1 [Reference]	1 [Reference]
Twins or higher-order birth	229	72 (31.4)	1.07 (0.88–1.31)	1.03 (0.84–1.27)
Unknown/missing	8	5 (62.5)	NC	NC
Maternal race/ethnicity				
Non-Hispanic white	2285	645 (28.2)	1 [Reference]	1 [Reference]
Non-Hispanic black	368	109 (29.6)	1.05 (0.88–1.24)	1.20 (0.99–1.44)
Hispanic	840	281 (33.5)	**1.19 (1.06–1.33)**	1.18 (1.00–1.39)
Other/unknown	253	71 (28.1)	0.99 (0.81–1.22)	1.06 (0.85–1.32)
Maternal age at delivery, y				
≤24	1151	356 (30.9)	1 [Reference]	1 [Reference]
25–34	2014	605 (30.0)	0.97 (0.87–1.08)	0.96 (0.84–1.08)
≥35	581	145 (25.0)	**0.81 (0.68–0.95)**	0.87 (0.72–1.05)
Maternal education				
Less than high school graduate	636	204 (32.1)	1 [Reference]	1 [Reference]
High school graduate or equivalent	908	274 (30.2)	0.94 (0.81–1.09)	1.09 (0.92–1.29)
College or university, some or graduate	2132	607 (28.5)	0.89 (0.78–1.01)	1.08 (0.92–1.28)
Unknown/missing	70	21 (30.0)	NC	NC
Maternal prepregnancy BMI[e]				
<18.5 (Underweight)	193	47 (24.4)	0.84 (0.65–1.09)	0.79 (0.61–1.02)
18.5–24.0 (Normal weight)	1800	523 (29.1)	1 [Reference]	1 [Reference]
25.0–29.0 (Overweight)	839	257 (30.6)	1.05 (0.93–1.19)	1.07 (0.95–1.21)
≥30.0 (Obese)	733	218 (29.7)	1.02 (0.9–1.17)	1.02 (0.89–1.18)
Unknown/missing	181	61 (33.7)	NC	NC
Diabetes mellitus diagnosis before or during index pregnancy[f]				
No	3301	977 (29.6)	1 [Reference]	1 [Reference]
Yes	420	122 (29.0)	0.98 (0.84–1.15)	0.91 (0.77–1.08)
Unknown/missing	25	7 (28.0)	NC	NC
Hypertension at any time				
No	3183	908 (28.5)	1 [Reference]	1 [Reference]
Yes	554	195 (35.2)	**1.23 (1.09–1.40)**	1.08 (0.95–1.23)
Unknown/missing	9	3 (33.3)	NC	NC
Maternal fertility treatments				

Characteristic	No. (%) of Infants		PR (95% CI)	
	Total	Late Detection[b]	Crude Analysis	Adjusted Analysis
No	3493	1032 (29.5)	1 [Reference]	1 [Reference]
Yes	200	58 (29.0)	0.98 (0.79–1.23)	1.03 (0.83–1.29)
Unknown/missing	53	16 (30.2)	NC	NC
Previous pregnancy losses				
None	2361	707 (29.9)	1 [Reference]	1 [Reference]
1	853	241 (28.3)	0.94 (0.83–1.07)	0.93 (0.82–1.05)
2	324	94 (29.0)	0.97 (0.81–1.16)	1.04 (0.87–1.24)
≥3	189	59 (31.2)	1.04 (0.84–1.30)	1.06 (0.85–1.31)
Unknown/missing	19	5 (26.3)	NC	NC
First prenatal care visit				
First trimester	3104	909 (29.3)	1 [Reference]	1 [Reference]
Second trimester	415	127 (30.6)	1.04 (0.90–1.22)	0.93 (0.80–1.09)
Third trimester	25	7 (28.0)	0.96 (0.51–1.80)	0.94 (0.48–1.81)
Unknown/missing	202	63 (31.2)	NC	NC
Study site				
A	537	117 (21.8)	1 [Reference]	1 [Reference]
B	582	146 (25.1)	1.15 (0.93–1.42)	1.17 (0.95–1.46)
C	460	123 (26.7)	1.23 (0.98–1.53)	1.18 (0.92–1.52)
D	383	105 (27.4)	**1.26 (1.00–1.58)**	**1.32(1.05–1.67)**
E	359	98 (27.3)	1.25 (0.99–1.58)	**1.40(1.11–1.77)**
F	229	67 (29.3)	**1.34 (1.04–1.74)**	**1.35 (1.04–1.75)**
G	329	104 (31.6)	**1.45 (1.16–1.82)**	**1.40 (1.10–1.79)**
H	465	174 (37.4)	**1.72 (1.41–2.10)**	**1.75 (1.41–2.17)**
I	402	172 (42.8)	**1.96 (1.61–2.39)**	**2.09 (1.66–2.63)**

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCHD, critical congenital heart disease; NC, not calculated; PR, prevalence ratio.

[a] Adjusted results from a Poisson regression model with robust error variance that included all listed variables and excluded infants with at least 1missing value for any included variable. Boldface indicates statistically significant ($P < .05$).

[b] Defined as a diagnosis more than 3 days after birth via echocardiography or autopsy.

[c] Chromosomal abnormalities, single-gene disorders, and birth defects with known etiology are excluded from the National Birth Defects Prevention Study.

[d] Multiple CCHD refers to more than 1 screening-detectable CCHD.

[e] Calculated from self-reported height and weight.

[f] Includes types 1 and 2 and gestational.