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The National Birth Defects Prevention Study: a review of the methods

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Abstract

Background—The National Birth Defects Prevention Study (NBDPS) is a large population-based multi-center case-control study of major birth defects in the United States.

Methods—Data collection took place from 1998 through 2013 on pregnancies ending between October 1997 and December 2011. Cases could be live born, stillborn or induced terminations, and were identified from birth defects surveillance programs in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah. Controls were live born infants without major birth defects identified from the same geographical regions and time periods as cases via either vital records or birth hospitals. Computer-assisted telephone interviews were completed with women between 6 weeks and 24 months after the estimated date of delivery. After completion of interviews, families received buccal cell collection kits for the mother, father and infant (if living).

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Results—There were 47,832 eligible cases and 18,272 eligible controls. Among these, 32,187 (67%) and 11,814 (65%) respectively, provided interview information about their pregnancies. Buccal cell collection kits with a cytobrush for at least one family member were returned by 19,065 case and 6,211 control families (65% and 59% of those who were sent a kit). More than 500 projects have been proposed by the collaborators and over 200 manuscripts published using data from the NBDPS through December 2014.

Conclusion—The NBDPS has made substantial contributions to the field of birth defects epidemiology through its rigorous design, including case classification, detailed questionnaire and specimen collection, large study population, and collaborative activities across Centers.

Major structural birth defects are common, costly and critical. About three percent of all live births in the United States are affected by birth defects (Centers for Disease and Prevention, 2008); they account for one in five infant deaths (Xu and others, 2014) and contribute substantially to childhood morbidity and long-term disability. Most birth defects are due to unknown causes or a combination of causes (Nelson and Holmes, 1989), and because the etiologies of specific phenotypes may vary, it is important to study them in homogeneous groups. However, because individual types of birth defects are relatively rare, it has been difficult in the past to conduct a study large enough to provide the necessary statistical power to assess risk factors for individual defects.

In 1996, Congress appropriated funds to the U.S. Centers for Disease Control and Prevention (CDC) to establish the Centers for Birth Defects Research and Prevention. This funding was formalized by the Birth Defects Prevention Act of 1998. A Georgia Center was established at CDC and cooperative agreements awarded with competitive renewals to Centers in nine states during one or more cycles of the cooperative agreement. From 1997 to 2013, the primary collaborative activity of these Centers was a multi-center case-control study, the National Birth Defects Prevention Study (NBDPS). In this manuscript, we summarize the methods (Figure 1) used during the data collection phase of the NBDPS.

NBDPS Centers and population

Participating Centers had access to data from a birth defects surveillance program that used active case-finding for all major structural birth defects eligible for inclusion in the NBDPS (Table 1). Since each Center was expected to contribute about 300 cases per year, the minimum population base was 35,000 births per year. For most years of the study, the study sites covered a birth population between 35,000-80,000 births per year. Participating Centers were Arkansas (AR, statewide), California (CA, selected counties), Georgia (GA, selected counties), Iowa (IA, statewide), Massachusetts (MA, selected counties except for 16 months when it was statewide), North Carolina (NC, selected counties), New Jersey (NJ, statewide, some common defects were sampled), New York (NY, selected counties), Texas (TX, selected counties) and Utah (UT, statewide) (Figure A online). Abstractors at each of the birth defects surveillance programs went out to birth and children's hospitals to ascertain eligible birth defects. This information was then entered in the NBDPS clinical database for review.

There were changes in NBDPS Centers over time (Figure 2), NJ stopped contributing data in 2003, and NC and UT started contributing data in 2003. Case ascertainment procedures also changed over time for some Centers with respect to the inclusion of cases among live births, stillbirths and induced abortions, and the use of data sources specifically to ascertain prenatal diagnoses, such as specialized ultrasound clinics (Figure 2).

Study eligibility started with pregnancies ending on or after October 1, 1997 and concluded with pregnancies with estimated dates of delivery (EDD) on or before December 31, 2011. During this study period, there were approximately six million births in the NBDPS catchment areas. Each Center's surveillance program ascertained all case infants with NBDPS-eligible birth defects that occurred in the study region. All Centers included defects diagnosed at least until the child turned one year old; some Centers included defects diagnosed up to two years old. Control infants were randomly selected from among live born infants from the same study region as the cases; the monthly number of controls selected was proportionate to the number of births in the same month in the previous year. Control infants were selected from vital records (AR [2000-2011], GA [2001-2011], IA, MA, NC, NJ, UT) or from birth hospital records (AR [1997-2000], CA, GA [1998-2001], NY, TX). Each Center interviewed mothers of approximately 100 control infants each year. A woman was not eligible to participate in the NBDPS if she already participated with a previous pregnancy, could not complete the interview in English or Spanish, was incarcerated, or did not have legal custody of the child at the time of the interview. Due to state-specific requirements for obtaining informed consent from those who were less than 18 years old at the end of their pregnancy, 3 of 10 Centers did not include eligible women less than 18 years old at the time of interview.

Study coordination

The NBDPS was managed by staff of the Birth Defects Branch at CDC's National Center on Birth Defects and Developmental Disabilities. The study-wide principal investigator, project officer, study coordinator, biologics coordinator, Georgia principal investigator, and data managers were part of the CDC management team. A Coordinating Council, established in 2004, consisted of principal investigators from participating Centers; each Center had one vote. The Coordinating Council's charge was to oversee infrastructure, address managerial issues, and establish research priorities. The Coordinating Council communicated through monthly conference calls and an annual in-person meeting.

Several committees, comprised of individuals representing each Center, assisted with the coordination of NBDPS activities. The Clinicians Committee was composed of clinical geneticists who conducted case review and classification (described below). The Questionnaire and Methods Committee was responsible for ongoing quality control and improvements to the questionnaire and other aspects of the study protocol. The Interviewers and Study Coordinators Committee provided an opportunity for interviewers from different Centers to share their experiences and to be guided by peers and CDC staff on how to handle unique interviewing situations. The Biologics Committee, Epidemiologists/Analysts Committee, and the Data Sharing Committee have on-going activities even after the completion of data collection. The Biologics Committee continues to oversee the storage

and retrieval of biological specimens. The latter two committees are described in detail below.

Clinical NBDPS data: Case classification

For major structural birth defects included in the NBDPS (Table 1), all clinical information was reviewed by a clinical geneticist to confirm eligibility prior to requesting an interview. Because the goal of the study was to identify unknown causes of birth defects, cases with defects of known etiology, such as single gene conditions or chromosomal abnormalities were excluded.

The methodology for case classification has been described previously (Rasmussen and others, 2003). Cases were classified as isolated, multiple, or complex. A case was considered isolated if there was only one major defect diagnosed, regardless of whether minor defects were also diagnosed. If two or more major defects were diagnosed and the defects were developmentally related to one another, then the pattern of defects represented a sequence and the case was classified as isolated. When two or more major defects were diagnosed in the same organ system, the case was usually classified as isolated, with the exception being defects of the gastrointestinal tract. If two or more major defects occurred in different organ systems and the defects did not represent a sequence or a complex case, the case was classified as multiple. A complex case was defined as a pattern of major defects that are embryologically related and likely represent an early problem in morphogenesis, often akin to a developmental field defect. The causes of defects that are part of a complex case are generally not known, whereas patterns of defects that occur in sequences more often have a suspected cause (Table 2).

Some birth defect phenotypes were classified by the same clinical geneticist for all cases for the entire study period. For other defect types, classification was completed by more than one person, but the clinical geneticists developed guidelines that detailed the (1) inclusion and exclusion criteria for each defect eligible for the NBDPS; (2) rationale for including certain diagnostic codes for defects and related defects; (3) instructions and rationale for designating the final case classification (isolated, multiple, complex); and (4) instructions and recommendations to analysts on how the defect type could be analyzed in epidemiologic studies. For cases of congenital heart defects, four clinicians with expertise in pediatric cardiology and clinical genetics developed a classification of just the heart defects (Botto and others, 2007), and this classification was in addition to the classification of the overall constellation of defects that was completed by the clinical geneticists. Eligibility criteria for most defects were consistent over the study period, but for certain defects the criteria for inclusion in analyses changed (Table 3).

Causative genetic factors for some defects studied in NBDPS have been identified during the course of the NBDPS, necessitating changes in eligibility criteria. For instance, initially, the cause of CHARGE syndrome was not certain, and it was classified as an association (a group of anomalies that occur with a statistical clustering, but not representing a recognizable syndrome, sequence, or developmental field defect). Therefore, cases of potential CHARGE association having at least one NBDPS-eligible defect (e.g., choanal

atresia, heart defect) were included. Later, *CHD7* mutations were identified as causative for some cases of CHARGE syndrome (Vissers and others, 2004). Therefore, cases with the phenotype of CHARGE syndrome with EDDs prior to January 1, 2006 remained in the study, but cases with EDDs after January 1, 2006 that had a *CHD7* mutation were excluded. Cases with CHARGE syndrome phenotype that had no *CHD7* mutation identified or did not have mutation testing performed were included throughout the study.

Another area of technological development that impacted NBDPS case classification was the comparative genomic hybridization (CGH) microarray, used to identify submicroscopic gains or losses of chromosomal material. Because these microduplications or microdeletions are potentially causative for birth defects, eligibility criteria based on a consensus statement (Miller and others, 2010) were developed for cases of duplication or deletion identified by CGH microarray with EDDs on or after January 1, 2009. If a phenotypically normal parent had the identical microduplication or microdeletion, then the infant's defect was presumed to represent a benign copy number variant, and the case infant was included in the study. If neither parent had the microduplication or microdeletion, then the chromosomal anomaly was presumed to be *de novo* and potentially pathogenic, so the case was excluded. However, if parental studies were not performed, then the case was excluded from the study if at least one of the following criteria was met for the microduplication or microdeletion: (1) it was associated with a previously characterized phenotype; (2) it contained at least one gene known or strongly suspected to be dosage sensitive; or (3) it was >400 kb in size. If none of these 3 criteria was met for the microduplication or microdeletion, the case was included.

Interview recruitment

Contact information for women eligible for study participation could be obtained from three sources: the Center's birth defects surveillance program, hospital records, or state birth certificates. Individual Centers sent out the introductory packet 6 weeks or more after the EDD; interviews had to be initiated by 24 months after the EDD. The introductory packet contained a letter introducing the study, which was signed by the local principal investigator, a calendar to assist women in accurately reporting exposures relative to their timing during her pregnancy, a “Frequently Asked Questions” document, and a “Rights of Human Subjects” document and a twenty dollar incentive. Materials were developed in collaboration with all Centers to ensure that the same information was delivered in the same way, although modifications for locally relevant information were allowed when required by the local Institutional Review Board (IRB). All protocols, contact materials and the interview content were approved by the CDC IRB, the Office of Management and Budget (OMB), and the local IRB(s) for each Center. The contents of the introductory packet and other study materials and products underwent several improvements over the study period in an effort to update and unify the appearance of all NBDPS materials; consistent graphical elements and color schemes were developed to increase study recognition and to facilitate higher participation (online-only Figure B).

Interview Participation

Overall, of the women who were invited to participate, 67% of cases and 65% of controls decided to take part. Interviews were conducted at each of the sites, or through a contractor, and participation has varied over time and by Center. Over the course of the study, use of telephone landlines decreased while use of cell phones increased; cell phone numbers were not always available through traditional directories. Centers adapted to challenges in recruitment in a variety of ways, including the use of cell phones instead of landlines to initiate calls (in order to match the participant's cellular provider to avoid call charges) and e-mail to contact study participants. In an effort to understand the magnitude of potential selection bias due to nonresponse, Cogswell and colleagues (Cogswell and others, 2009) compared demographic characteristics of controls who participated (n=4,495) to all eligible controls (n=6,681), and to all live born infants in the base population from which the controls were selected (n=2,468,697). Compared with base populations, control participants did not differ substantively in distributions of maternal or paternal age, number of previous live births, maternal smoking, or diabetes, but they did differ in other maternal characteristics (i.e., race/ethnicity, education, entry into prenatal care), and infant characteristics (i.e., birth weight, gestational age, and plurality). Compared with eligible controls who did not participate, control participants differed in distributions of maternal, but not infant, characteristics. Overall the authors concluded that control participants were generally representative of their base populations.

Interview Revisions

The computer-assisted telephone interview (CATI) was administered to women with pregnancies ending on or after October 1, 1997. The original CATI (Yoon and others, 2001) included questions on a range of topics (Table 4). Substantial changes to the CATI were implemented beginning with births on or after January 1, 2006.

Based on research suggesting that stressful life events may be associated with the occurrence of birth defects (Carmichael and others, 2007; de Weerth and Buitelaar, 2005; Hansen and others, 2000), a new section was added to the CATI that asked mothers about stressful life events immediately before and during pregnancy, as well as the availability of social support. The caffeine questions were changed to account for early pregnancy changes in intake and to estimate portion size. Established associations of maternal diabetes and obesity with increased risk for birth defects (Correa and others, 2008; Waller and others, 2007) prompted the addition of questions regarding fat consumption, dieting behavior, changes in weight, more detailed questions regarding diabetes management, and, in 2010, the addition of physical activity questions. In an effort to limit the interview to one hour, when new questions were added in 2006, other questions were removed. Specifically, questions about prenatal diagnoses, paternal drug use, and maternal assessment of occupational exposure to specific chemicals were excluded. A section on water use and consumption was significantly shortened, and combined with questions on use of a hot tub, Jacuzzi, or sauna.

Buccal cell collection

To better understand the role that genetic and epigenetic factors play in the etiologies of birth defects, cytobrushes were used to collect buccal (cheek) cell samples from NBDPS family triads (case- and control-infants and their parents). Following the completion of the interview, women were mailed a buccal cell collection kit that included collection instructions, documents for informed consent, six cytobrushes (two each for the mother, the child (if living), and the father), and a postage-paid return mailer. A monetary incentive ($20 money order or check) was added to each kit beginning in 1999 or 2000, depending on the Center. In 2002, the kits were redesigned to provide better clarity, organization, and convenience (Online Figure B). Buccal cell collection kits were returned by 19,065 case families and by 6,211 control families (65% and 59% of those who received the kits, respectively).

Participation in buccal cell collection

In 2002, two Centers with low buccal cell collection participation began sending families an additional $20 incentive following the return of completed buccal cell collection kits, which resulted in increased participation. The success of the additional incentive led to its implementation by all Centers by 2008. Addition of the third incentive was particularly beneficial at Centers with the lowest participation, especially among some racial-ethnic groups, and participation across Centers increased by an average of 13 and 11 percentage points in case and control families, respectively.

To assess women's attitudes toward participation in buccal cell collection, six focus group discussions were held in September 2007 with women residing in metropolitan Atlanta, Georgia who had completed the NBDPS interview and either did or did not complete buccal cell collection (Jenkins and others, 2009; Jenkins and others, 2011). Four of the focus groups were comprised solely of non-Hispanic black women because they were the racial-ethnic group with the lowest participation. Barriers to participation reported by focus group participants included concerns about how they were identified, government involvement, potential misuse of the DNA specimens, not disclosing individual genetic results, sterility of cytobrushes sent through the mail, and paternal skepticism. Motivations for participation included having a child affected by a birth defect, researcher credibility, non-invasive collection methods, monetary incentives, professional-style study materials, and positive experiences with study interviewers. To address some of the barriers, NBDPS study materials were updated with information about how infants were identified, and a website was developed that included a video of buccal cell collection and information on the use, storage, and disposal of DNA specimens. To alleviate concerns over cytobrush sterility, “Sterile if package is unopened” was added to the cytobrush packaging.

Glidewell and colleagues (Glidewell and others, 2013) examined factors associated with participation in buccal cell collection in the NBDPS. Buccal responders were more likely to be non-Hispanic white, older case mothers with higher education, higher household incomes, pregnancies that were intended, to have had a shorter interval between their EDD and interview date, to have received a redesigned buccal cell collection kit and an additional

$20 incentive, to have consumed folic acid and not to have smoked cigarettes during the periconceptional period.

Buccal cell specimen quality

In response to concerns about DNA degradation during transit, cytobrushes packaged in closed plastic containers were replaced with cytobrushes packaged in paper-backed peel pouches in mid-2003. The impact of cytobrush packaging on the yield and quality of self-collected buccal cell-derived DNA was assessed (Gallagher and others, 2011; Krakowiak and others, 2003). Higher median human-specific DNA yields (1300ng vs. 60ng) and more successful short tandem repeat (STR) amplification rates (99.5% vs 59.5%) were observed when DNA was extracted from cytobrushes transported in the new pouches that allowed air-drying when compared to DNA extracted from cytobrushes transported in closed plastic containers.

To further improve DNA specimen quantity and quality, some families who previously submitted closed container cytobrushes were asked in 2006-2008 to collect new specimens using cytobrushes packaged in paper-backed peel pouches. Eligible families had pregnancies affected by spina bifida, gastroschisis, or longitudinal limb defects; and an equal number of control families were also invited. Return rates (families who returned kits /eligible families) varied by Center and case-control status (20%–83% for cases; 13%–63% for controls).

Centralized DNA processing laboratory

When DNA collection via cytobrushes was initially integrated into the NBDPS, DNA was extracted at each Center using different methods, and short tandem repeat (STR) markers were amplified using two sets of primer pairs (Figure 3). Quality control (QC) criteria included successful polymerase chain reaction (PCR) amplification after at least two attempts with at least one STR marker and alleles consistent with the reported family relationship. If those standards were met, DNA extracted from one cytobrush was divided into 10 or 20 aliquots of equal size and the aliquots were shipped to the central biorepository. DNA from the second cytobrush was retained at the local Center. In 2003, a centralized laboratory was established at the CDC to improve consistency and standardize extraction and QC methods (Figure 3). One cytobrush from each NBDPS participant was retained at the local Center, but the second cytobrush was sent to the centralized laboratory at CDC for DNA extraction using either a phenol-chloroform method (Garcia-Closas and others, 2001) or Gentra Puregene® (QIAGEN®); human genomic DNA (gDNA) yields were assessed by quantitative real-time PCR using the human RNaseP gene, and three or four STR markers were used to assess DNA quality. DNA specimens that met QC criteria (human gDNA concentration ≥0.1 ng/μl, successful PCR amplification after at least two attempts with at least one STR marker, and alleles consistent with the reported family relationship) were divided into two aliquots of equal size and shipped to the central biorepository. Both before and after establishment of the centralized lab, if a specimen did not meet QC criteria, the family was contacted and asked to provide additional specimens; however, due to low return rates and lack of resolution of the initial inconsistencies with recollected specimens, as of 2005, families whose alleles were not consistent with the

reported family relationship (i.e. non-paternity) were not asked to provide additional specimens.

External genotyping quality assessment

To ensure proficiency of laboratories genotyping NBDPS buccal-derived DNA specimens independent of source material, NBDPS genotyping laboratories annually genotyped a standard single nucleotide polymorphism (SNP) set on a subset of the Coriell Institute for Medical Research's Polymorphism Discovery Resource (PDR) DNA specimens (Collins and others, 1998). The SNP set was determined by the NBDPS Genetic Analysis Working Group and included SNPs assayed by multiple labs and at least one SNP with publicly available genotypes. Standard 96-well plates that include 86 PDR specimens, four replicates, two negative controls, and four empty wells for internal laboratory genotyping controls were plated by Coriell and sent directly to each NBDPS laboratory. Plate formats and content were changed yearly. Laboratories were blinded to specimen type and reported genotyping results centrally to the CDC for analysis. After implementation of annual external quality assessment (EQA), call rates of 97-100% were reported across NBDPS laboratories. Concordance of 99-100% was reported between NBDPS laboratories and between NBDPS laboratories and the publicly available genotypes.

To assure data quality across laboratories using arrays from higher throughput platforms, NBDPS genotyping laboratories ran assays on a set of paired cytobrush buccal- and whole blood-derived DNA samples from 6 parent-offspring trios ascertained through the University of Washington under an IRB-approved protocol, prior to implementation of each new project. Laboratories planning to use whole genome amplified (WGA) products were required to run assays using paired gDNA and WGA products. After implementation of annual EQA, call rates of 92-100% were reported across NBDPS genotyping laboratories. Concordance between paired blood-buccal samples was 100% pre- and post-WGA. Inter-laboratory concordance for variants assayed in common was 100%. Additionally, SNP genotyping was consistent with Mendelian inheritance.

Data management

NBDPS data were stored in three major database types: the clinical databases, containing the abstracted case data; the CATI databases; and the biologic sample databases. Centers transferred data to CDC monthly to ensure the central databases were current, and to reduce the chance of substantial data loss in case of database corruption. Each Center first deposited all three current databases on CDC's secure data network; then CDC programmers added any new data to the central databases and then placed updated files for each Center in their private folder on the secure data network.

Analysis of NBDPS data is on-going. Data are accessible to NBDPS collaborators through the Data Analysis Tools (DAT), a Microsoft Access database. The DAT is a centralized effort that serves to improve data quality and efficiency of analyses conducted by investigators in different Centers. The DAT enables NBDPS analysts in all Centers to create datasets that contain only those variables that will be used for an approved project. The DAT includes a data dictionary, which provides variable names, definitions, and formatting

information. The DAT contains a set of calculated variables created by combining several interview questions, including maternal age at delivery, maternal body mass index, indicators for whether the mother used alcohol or cigarettes during the periconceptional period, maternal diabetes status, and use of folic acid supplements. The DAT does not contain any names, addresses or geocodes. A specific tool using the medication database from the Slone Epidemiology Center at Boston University allows analysts to create exposure variables for specific medications or all medications with a specific component, and to define the exposure period of interest for that medication. Data from the food frequency section, which pertained to the year before pregnancy, was used in combination with data from the United States Department of Agriculture to assign levels of nutrient and calorie intake with the assistance of North Carolina Department of Nutrition Clinical Research Center, Nutrition Epidemiology Core. Analysts communicate through monthly conference calls of the Epidemiologists/Analysts Committee, a listserv and a SharePoint site. And, as a quality control measure, each analysis is replicated by an independent analyst prior to submission for publication.

The Data Sharing Committee for NBDPS has two major responsibilities: the ongoing task of deciding how data will be equitably shared for analysis and providing abstract and manuscript review prior to submission to scientific meetings or journals. This committee consists of principal investigators or co-investigators from each Center. Obtaining approval to conduct an NBDPS analysis is a two-step process. First, a two-page letter of intent is submitted containing scientific background/justification, a brief summary of the analytical plan and any conflicts with existing NBDPS analytic projects. Upon approval by the Committee, the lead investigator then submits a more detailed proposal. The proposal must contain a detailed analytical plan, including power calculations. The Committee requires annual updates from the lead investigator on the progress of each project. As of December 2014, there were more than 520 proposed projects. Senior investigators are requested to serve as NBDPS data sharing editor for six-month periods of time, where they coordinate the anonymous review of all NBDPS manuscripts. Review of abstracts to be submitted to scientific meetings is coordinated at the CDC.

Investigators from outside NBDPS who are interested in analyzing NBDPS data must collaborate with one of the NBDPS principal investigators, or they can write a letter to the Data Sharing Committee describing their research interest. The committee will let the researcher know if their interest is already covered under an existing proposed project or will forward it to NBDPS researchers interested in that topic in order to establish a formal collaboration. Collaboration with external investigators in this manner is encouraged.

Expanded occupational and environmental data

Through an agreement with the CDC's National Institute for Occupational Safety and Health (NIOSH), industrial hygienist contractors at Battelle and occupational epidemiologists at the NIOSH have used the responses to the maternal occupation sections of the NBDPS CATI to create an occupational exposure database. The database includes the estimated frequency, intensity, and duration of job exposures for over 10,000 respondents. The occupational team estimated quantified exposure to occupational chemicals including pesticides, chlorinated

and aromatic solvents, polycyclic aromatic hydrocarbons, and heavy metals, resulting in several publications ((Kielb and others, 2014; Lupo and others, 2012; Rocheleau and others, 2011)).

Combining residential locations with other geographic data may inform environmental exposures such as air pollution. Therefore the NBDPS questionnaire included a complete residential history, from three months before conception through the date of delivery. Women were asked to report, to the best of their ability, the exact street address of each residence. To ensure the application of a uniform data cleaning and geocoding method, CDC requested that all NBDPS residential address data be centrally geocoded by the Agency for Toxic Substances and Disease Registry's Geographic Research, Analysis and Services Program. To protect participant privacy, CDC returned geocoded address data to the respective Centers, but this data can be requested for specific projects (Stingone and others, 2014).

Limitations of NBDPS

There were several limitations of the NBDPS. The first is that, on average only about two-thirds of invited women participated, which could potentially introduce selection bias if nonparticipants had substantially different risk profiles from those who participated. NBDPS control participants were older, more often non-Hispanic white and more highly educated than non-participants (Cogswell and others, 2009). The fact that the inclusion of stillbirths and induced abortions changed over the data collection period is a limitation, as is the to-be-expected difference in participation based on the pregnancy outcome. Another limitation was that exposure information was self-reported. Recall of the timing and duration of exposures occurring up to 2 years in the past was challenging for some participants, especially for items requiring detailed information. Recall of use of over-the-counter and prescription medications during early pregnancy, is of particular concern. To optimize recall, women were first asked about specific diseases or medical conditions and then asked about medication use to treat conditions. In addition, women were asked about specific medications using a list of specific medication names, without reference to diseases or conditions. However, NBDPS did not capture information on medication dose, and for those medications that were reported in response to the medication list, there was no information about the indication for use. For some exposures, validation studies were conducted. One such project compared fertility treatment data reported by assisted reproductive technology clinics to NBDPS participants' responses to questions about fertility treatment use (Liberman and others, 2014). Using the clinic data as the gold standard, the sensitivity of maternal report for use of in vitro fertilization (IVF) was 91%. Another validation study compared responses to CATI questionnaire items regarding smoking to data on birth certificates; smoking was more often reported in the NBDPS (Srisukhumbowornchai and others, 2012). Another study conducted a Bayesian bias analysis which incorporated previous research on reliability of self-reported smoking to examine the relationship of smoking and orofacial clefts reported from the NBDPS (Honein and others, 2007; MacLehose and others, 2009). Smoking recall bias has been raised as a concern in previous studies looking at the smoking-orofacial cleft association. After correcting for potential

misclassification using bias modeling, this study found the likely levels of bias did not impact the relationship between smoking and orofacial clefts in NBDPS.

Lessons learned

The NBDPS has provided an unprecedented level of information for studying birth defects and for learning best practices for future birth defects research. A major strength of the study, in addition to its sample size, was the successful collaboration with multi-disciplinary teams across 10 Centers in the United States. Consistency of study methods across the sites, particularly use of the same case inclusion criteria and interview instrument allowed for the creation of a pooled dataset for analysis that is both large and internally consistent. Multiple levels of case review including a study-wide central review ensured consistency in determining case eligibility and classification. Providing centralized data management with monthly replication safe-guarded the data. One particularly beneficial lesson learned regarding buccal cell DNA collection was letting brushes air dry, which resulted in higher DNA yields and better quality DNA. A last key step in fostering this collaboration was establishing clear data sharing guidelines. Clear rationale for undertaking a project as well as critical feedback at the start of projects resulted in a more efficient review process and higher quality manuscripts.

The NBDPS has moved the field of birth defects epidemiology forward since its launch in 1996. Over 44,000 women with pregnancies in 1997-2011 participated in the study. To date, more than 350 interdisciplinary researchers have collaborated on more than 200 peer-reviewed manuscripts. The study has provided training opportunities where many masters-level students have learned about reproductive epidemiology working on NBDPS analyses and at least six doctoral dissertations have been completed using NBDPS data. And this is only the beginning. Papers on genetic risk factors for birth defects are beginning to be published using data from the NBDPS – and there are many more genetic, environmental, and gene-environment interaction analyses being planned. NBDPS will be a rich source of epidemiological and genetic data to study risk factors for birth defects for many years to come.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1.	Pregnancies affected by one or more of the NBDPS-eligible birth defects were identified by each Center's surveillance program. Live born control infants were identified via birth certificates or birth hospitals.
2.	Case information was obtained from surveillance programs, which included clinical information abstracted from case medical records and entered into a clinical database developed at the CDC. The electronic clinical record of each case was reviewed by a board-certified clinical geneticist who determined whether the case was eligible to participate in the study. Mothers of case and control infants who were deemed eligible were contacted; address information was reviewed to ensure the woman was a resident in the defined study region at the end of the pregnancy.
3.	An informational packet, including a $20 money order or check, was mailed to eligible participants to introduce the study and inform her that she would receive a phone call to request her participation in the National Birth Defects Prevention Study.
4.	A trained interviewer at the local Center or a contracting facility called the mother to request verbal consent to complete the computer-based telephone interview, either during one or multiple phone calls. Interviews were completed in English or Spanish.
5.	Approximately one week after completing the interview, the mother received a thank-you letter with an NBDPS newsletter and a packet containing cytobrushes (two per individual) to collect buccal (cheek) cells from herself, her infant (if living), and the infant's father; a written consent form and a second $20 money order or check accompanied the buccal packet.
6.	Upon return of the cytobrushes, the mother received a final thank-you letter and a third $20 money order or check.
7.	Clinical, interview and biologic data were sent via a secure data network from each Center to the CDC on a monthly basis to be included in study-wide central databases. These datasets did not include names or addresses.
8.	Open-ended interview questions were coded using NBDPS-specific code lists or existing coding schemes such as Standard Occupation Classification (SOC) codes.
9.	Analytical databases that included cleaned and coded interview data for complete years defined by estimated dates of delivery (EDDs) were created on an approximately annual basis.
10.	Occupational data was used to assess chemical exposure levels, geocoding was done on all residential addresses during pregnancy and food frequency information was translated to caloric intake.
11.	The final classification for each case within a specific phenotype was reviewed by a panel of clinical geneticists to ensure consistency across Centers and to assign the case to the appropriate defect categories if multiple defects were present.
12.	DNA was extracted from buccal cells and initial quality control assays were completed. Of the two cytobrushes submitted for each individual, DNA from one was stored at the originating Center and DNA from the other brush was stored in a central biorepository until requested by investigators for specific projects.
13.	Epidemiological and genetic analyses are ongoing.

Figure 1.
Basic study process for the National Birth Defects Prevention Study (NBDPS)

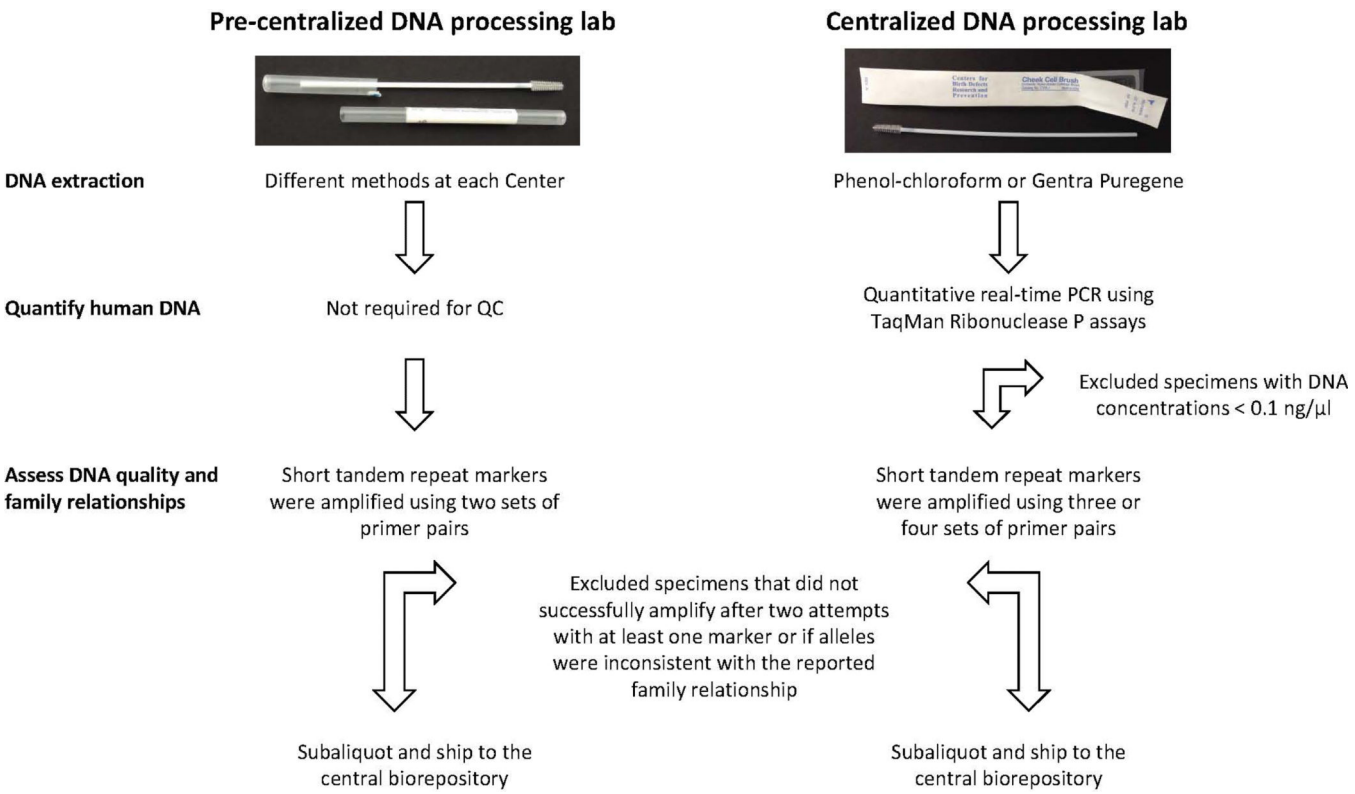

Figure 2.

Inclusion of cases among live births, stillbirths and induced abortions, and data sources used specifically to ascertain prenatal diagnoses, by estimated year of delivery and Center.

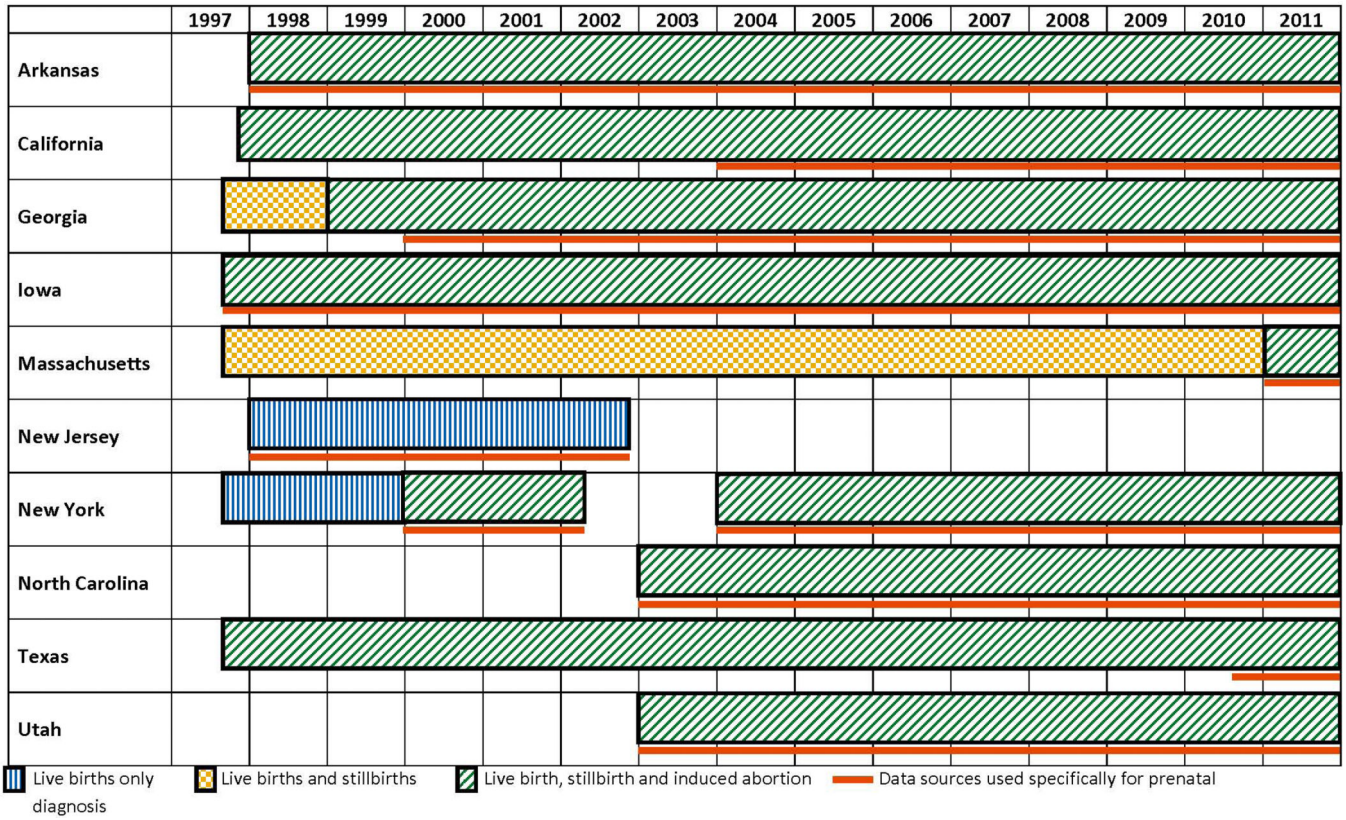

Figure 3.

Comparison of DNA extraction and quality control completed at each Center (pre-centralized DNA processing lab) and at the centralized DNA processing lab on samples that were sent to the repository.

Table 1

Number of case and control subjects eligible to be included and interviewed in the National Birth Defects Prevention Study, 1997-2011[a]

Birth Defects	Eligible(n)	Interviewed (n)	Birth Defects	Eligible (n)	Interviewed (n)
Total cases	**47832**	**32187**			
Controls	**18272**	**11814**			
Amnion rupture sequence	590	383	Craniosynostosis	2611	1794
Anencephaly, craniorachischisis	1164	687	Diaphragmatic hernia	1328	907
Spina bifida	1854	1334	Sacral agenesis	175	123
Encephalocele, encephalomyelocele	431	264	Omphalocele	747	503
Holoprosencephaly	321	181	Gastroschisis	2305	1504
Hydrocephalus	995	573	Laterality defects, heterotaxia	683	433
Dandy-Walker malformation	417	268	Ventricular septal defect (VSD)[e]	2693	1798
Anophthalmia, microphthalmia	411	281	Atrial septal defect (ASD)[f]	7280	4629
Cataracts[b]	668	434	Truncus arteriosus	309	211
Glaucoma, other anterior chamber eye defects[b,c]	323	190	D-transposition great arteries/Double outlet right ventricle	1731	1249
Anotia, microtia	1056	709	Tetralogy of Fallot	2041	1445
Choanal atresia	262	182	Single ventricle	413	276
Cleft lip with and without cleft palate	4537	3263	Atrioventricular septal defect[g]	1254	826
Cleft palate	2363	1651	Aortic stenosis	938	650
Esophageal atresia with and without tracheoesophageal fistula	1031	769	Coarctation of the aorta	2464	1730
Biliary atresia	315	216	Hypoplastic left heart syndrome	1034	724
Intestinal atresia or stenosis[d]	3342	2269	Pulmonary stenosis (valvar)	3023	2019
Hypospadias (second- or third-degree)	4061	2630	Pulmonary atresia (not tetralogy of Fallot variant)	679	453
Renal agenesis or hypoplasia (bilateral)	366	203	Tricuspid atresia	428	297
Bladder exstrophy	105	77	Ebstein malformation	330	208
Cloacal exstrophy, persistent cloaca	142	101	Anomalous pulmonary venous return	993	647
Limb deficiency (intercalary)	103	68			
Limb deficiency (longitudinal)	895	587			

Birth Defects	Eligible(n)	Interviewed (n)	Birth Defects	Eligible (n)	Interviewed (n)
Limb deficiency (transverse)	1603	1077			

[a] An infant with more than one eligible birth defects is counted in each eligible category

[b] Included in the study as of January 1, 2000

[c] Includes absence of the lens, spherical lens, lens coloboma, aniridia, Peters anomaly, Axenfeld anomaly, and Rieger anomaly

[d] Includes stenosis or atresia of the small intestine, large intestine, or rectum, and atresia of the anus

[e] Includes muscular VSD, perimembraneous/membraneous VSD, and VSD not otherwise specified

[f] Includes secundum ASD, other specified ASD, and ASD not otherwise specified; does not include primum ASD

[g] Includes primum ASD

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Table 2

Complex cases in the National Birth Defects Prevention Study and the birth defect category within which they are analyzed

Sequence	Birth Defect category
Amniotic band (AB) limb defects +/− AB craniofacial malformations	Amnion rupture sequence
Limb-body wall complex	Amnion rupture sequence
Urorectal septum malformation sequence	Intestinal atresia or stenosis
Imperforate anus-sacral anomalies	Intestinal atresia or stenosis
Omphalocele-Exstrophy-Imperforate anus-Spina bifida (OEIS complex)	Cloacal exstrophy, persistent cloaca
Pentalogy of Cantrell	Diaphragmatic hernia, Heart defects, and Omphalocele
Heterotaxy	Laterality defects, heterotaxia
Sacral agenesis with caudal regression	Sacral agenesis

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Table 3

Birth defects with eligibility changes for inclusion in the National Birth Defects Prevention Study

Birth Defect	Date of Eligibility Change(s) (EDD)	Criteria Prior to Change	Criteria After Change
Aneurysm of atrial septum with shunt	1/1/2006	Cases were included in the study and coded as atrial septal defect secundum type.	Cases of isolated aneurysm of the atrial septum with atrial shunt were excluded from the study.
Atrial septal defect, secundum type (ASD2) or not otherwise specified (ASD, NOS)	1/1/2006	All isolated ASD2 and ASD, NOS were included in the study.	Cases of isolated ASD2 or ASD, NOS were excluded from the study if (1) the diameter of the defect was ≤4 mm; (2) no size was provided for the defect, but it was described as “small,” “mild,” or “trivial;” or (3) no size or description of the defect was provided, and the only echocardiograms identifying the defect were performed when the infant was <6 weeks of age.
Cataract	1/1/2006	Cases with a family history consistent with Mendelian inheritance were included in the study, but they were classified as “syndromic” so as not to be included in risk factor analyses.	Cases of isolated cataract that had a first-degree relative with congenital cataract were excluded from the study.
Craniosynostosis	1/1/2003 and 11/1/2005	Presumptive isolated cases without confirmation by head computerized tomography (CT) or x-ray report were excluded from the study.	Presumptive cases without confirmation by head CT or x-ray report, but with a corrective surgical procedure for craniosynostosis were included in the study after 1/1/2003. Presumptive cases without confirmation by head CT or x-ray report, or surgery, but with histopathological diagnosis based solely on autopsy were included in the study after 11/1/2005.
Duodenal atresia	1/1/2006	Isolated cases associated with duodenal web were excluded from the study.	All cases of isolated duodenal atresia, type I, including those described as duodenal web, membrane, diaphragm, or windsock, were included in the study.
Pulmonary stenosis (valvar)	1/1/2005	All cases were included in the study.	Cases of isolated pulmonary valve stenosis were excluded from the study if one of the criteria was met: (1) peak gradient on echocardiogram or cardiac catheterization of < 15 mmHg; or (2) no peak gradient information, but the defect was described as “trivial,” “whiff,” or “mild.” However, cases that met one of the exclusion criteria, but had an abnormal pulmonary valve (described as thickened, dysplastic, doming in systole, etc.) were still included in the study.
Ventricular septal defect (VSD) muscular type or VSD not otherwise specified (VSD, NOS)	10/1/1998 and 1/1/1999	Muscular VSD and VSD, NOS without another NBDPS-eligible defect (isolated cases) were included in the study	Isolated cases of muscular VSD and VSD, NOS were excluded from the study if the EDD was after 10/1/1998 for cases from California, Georgia, Iowa, Massachusetts, New York and Texas, or after 1/1/1999 for cases from Arkansas and New Jersey.
Ventricular septal defect, other subtypes (e.g., canal type VSD, perimembranous VSD, malalignment VSD)	1/1/2006	Isolated VSD, other subtypes, without another NBDPS-eligible defect (isolated cases) were included in the study	VSD, other subtypes, without another NBDPS-eligible defect (isolated cases) were excluded from the study.

Table 4

Computer-assisted telephone interview (CATI) sections in the order they were asked for the periods 1997-2005 and 2006-2011

CATI 1997-2005	CATI 2006-2011
Index pregnancy	Index pregnancy Previous pregnancies Addresses during pregnancy Contraception Prenatal care Fertility treatments - mother Fertility treatments - father Morning sickness Diarrhea Dieting Weight gain/loss during pregnancy
Maternal health	Maternal health
Pregnancy history Previous pregnancies Weight gain/loss Contraception Fertility treatments - father Fertility treatments - mother Morning sickness Morning sickness weight loss Prenatal care Medication	Medication
Vitamins	Vitamins
Food frequency	Food frequency
Tobacco	Stress
Alcohol	Tobacco
Substance abuse	Alcohol
Home environment Addresses during pregnancy Hot tub/sauna use	Substance abuse *Reduced questions about father*
Mother's occupation	Water use *(reduced)*
Father's occupation	Mother's occupation

CATI 1997-2005	**CATI 2006-2011**
Family demographics - mother	Father's occupation
Family demographics - father	Physical activity *(added for interviews after 10/1/2010)*
Home water environment	Family demographics - mother
Drinking water at home	Family demographics - father
Drinking water at work/school	Family information - mother and father
Home water use	Closing/debriefing
Swimming pool use	
Closing/debriefing	

Note: A PDF of the most recent version of each of these two CATIs is available upon request from the corresponding author.