



Practice of Epidemiology

Control Selection and Participation in an Ongoing, Population-based, Case-Control Study of Birth Defects

The National Birth Defects Prevention Study

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To evaluate the representativeness of controls in an ongoing, population-based, case-control study of birth defects in 10 centers across the United States, researchers compared 1997–2003 birth certificate data linked to selected controls ($n = 6,681$) and control participants ($n = 4,395$) with those from their base populations ($n = 2,468,697$). Researchers analyzed differences in population characteristics (e.g., percentage of births at $\geq 2,500$ g) for each group. Compared with their base populations, control participants did not differ in distributions of maternal or paternal age, previous livebirths, maternal smoking, or diabetes, but they did differ in other maternal (i.e., race/ethnicity, education, entry into prenatal care) and infant (i.e., birth weight, gestational age, and plurality) characteristics. Differences in distributions of maternal, but not infant, characteristics were associated with participation by selected controls. Absolute differences in infant characteristics for the base population versus control participants were ≤ 1.3 percentage points. Differences in infant characteristics were greater at centers that selected controls from hospitals compared with centers that selected controls from electronic birth certificates. These findings suggest that control participants in the National Birth Defects Prevention Study generally are representative of their base populations. Hospital-based control selection may slightly underascertain infants affected by certain adverse birth outcomes.

case-control studies; congenital abnormalities; selection bias

Abbreviations: NBDPS, National Birth Defects Prevention Study; SPR, selection probability ratio.

The validity of findings from case-control studies is dependent on the selection of an appropriate control group (1, 2). For studies in which complete case ascertainment of a population is achievable, the use of a randomly selected control group representative of that population, so-called primary-base controls, has several advantages, as detailed in previous publications (1–3). Controls are likely to have a “base experience” comparable to that of the cases, that is, as members of the same source population, during the same time periods, as the eligible cases (3, 4). The study base can encompass the same exclusion criteria. Finally, the distribu-

tion of exposures among the controls is likely to be representative of the exposures in the general population. Thus, information about prevalence of specific risk factors may be generalizable to the base population and can be used to estimate the attributable fraction of disease related to specific exposures (3).

The National Birth Defects Prevention Study (NBDPS) was designed to identify all infants with major birth defects (cases) within a base population and to evaluate genetic and environmental factors associated with their occurrence (5). NBDPS is an ongoing, population-based, case-control study

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comprising data collected by birth defects surveillance systems within specified geographic areas in 10 US states. Cases have one or more of over 30 eligible birth defects and include liveborn or stillborn infants and electively terminated fetuses. Controls are unmatched to cases and are liveborn infants selected from the same base population as cases, with no major birth defects and with an estimated date of delivery within the same year as cases. Controls are either 1) randomly selected from birth certificates or 2) selected from birth hospitals by using a stratified, random sampling scheme.

In NBDPS, use of a control group representative of the base population also provides a unique opportunity to examine the prevalence of exposures to a variety of risk factors for adverse pregnancy outcomes during the periconceptional period (6–9). Given the desire to estimate the prevalence of exposure within a base population, information about the representative nature of study controls becomes important not only for internal validity of study findings but also for generalizability (3, 10). Representativeness can be influenced by how controls were originally selected and be further influenced by participation (1, 11).

The main objective of this analysis was to determine whether control participants represented liveborn infants within their base population and whether this differed by center selection method (hospital records or electronic birth certificates). To accomplish this objective, we 1) compared the sociodemographic and health characteristics of selected controls and control participants with those of their base population, 2) compared characteristics of control participants and control nonparticipants (i.e., controls selected but not interviewed), and 3) stratified analyses by center selection method. In addition, we compared characteristics of NBDPS control participants with those of the US population of livebirths during the same time period to assess generalizability of exposure prevalence to the US population.

MATERIALS AND METHODS

NBDPS began on October 1, 1997, and is ongoing. Cases are identified by using standard criteria from birth defect surveillance systems for each of 10 Centers for Birth Defects Research and Prevention (centers) (Arkansas, California, Georgia (metropolitan Atlanta), Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah). New Jersey ascertains cases from only liveborn infants. New York ascertained cases from only liveborn infants until 2000 but, since January 2000, has ascertained cases from liveborn and stillborn infants. All 8 other centers ascertain cases from liveborn and stillborn infants. Arkansas, California, Georgia, Iowa, North Carolina, Texas, and Utah also ascertain cases from elective terminations. New York ascertained cases from elective terminations starting in January 2000. New Jersey stopped data collection for NBDPS in September 2002, and North Carolina and Utah joined NBDPS in 2003 and contribute fewer data to the overall sample.

Each center selects all eligible cases and approximately 150 eligible controls each year for inclusion in the study in anticipation of a 70% participation rate. Eligible birth de-

fects are described elsewhere (5). Data abstracted for each selected case and control include, but are not limited to, contact information; maternal age at delivery; and infant gestational age at birth, birth weight, and plurality. Cases are ineligible for NBDPS if the infant has one or more of the following characteristics: stillborn at a gestational age of ≤ 20 weeks and birth weight of ≤ 500 g, birth defect other than those eligible, or born to a woman who resided outside the study area at delivery. Controls are ineligible for NBDPS if the selected infant has one or more of the following characteristics: not liveborn, a major birth defect, or born to a woman who resided outside of the study area at delivery. Selected controls are compared with the center's birth defects registries to exclude infants with birth defects. Potential cases and control participants are excluded at the time of the interview if the mother did not speak English or Spanish, previously participated in NBDPS, is incarcerated, is a donor or surrogate parent, is unable to answer the questions, or is deceased; or if the infant is in foster care or adopted. If a control mother had multiple infants, the firstborn baby is selected.

After addresses are confirmed, case and control mothers are mailed an introductory letter, a pamphlet, a fact sheet about the study, and a \$20 money order. Mothers are then called by trained interviewers, who describe the study according to a standardized script and ask the mother to participate. Mothers who consent are interviewed by telephone 6 weeks–24 months after the estimated date of delivery (3). For example, the mother of an infant with an estimated date of delivery of December 31, 2003, could be interviewed until December 31, 2005.

Within the base population, 3 centers randomly select controls from hospital records by month and birth hospital weighted by the number of births per hospital per year. Five centers randomly select controls from electronic birth certificates, and 2 centers used hospital selection at the beginning of the study and then switched to birth certificate selection (refer to Table 1 for selection strategies by center).

For this evaluation of controls, we used natality data on livebirths from each of the base populations of the 10 centers for their time periods of participation in NBDPS up to December 31, 2003, and for all US livebirths from October 1, 1997, through December 31, 2003. Each center linked natality data from birth certificates to the information collected on control infants selected for NBDPS. Centers used either birth certificate numbers or probabilistic methods and hand matching to link data. Excluding New Jersey, we linked 100% of records from control infants selected from birth certificates and more than 95% of records from control infants selected from hospital records. New Jersey did not link their data to birth certificates; thus, we used published state data and the limited data available from the clinical database (e.g., maternal age, infant birth weight, gestational age at birth, and plurality). We excluded New Jersey from the overall analyses because of the limited number of socio-demographic and health characteristics available for comparison.

Each center used statistical software to tabulate sociodemographic and health characteristics for 3 groups: their 1) base population, 2) selected controls, and 3) control

Table 1. Base Population, Selected Controls, and Control Participants, National Birth Defects Prevention Study, United States, October 1997–December 2003

State	Geographic Area	EDD	Selection Strategies ^a	Base Population, ^b No.	Selected Controls, ^c No.	Control Participants, ^d No.	Control Participants ÷ Selected Controls, %
Arkansas	Statewide	January 1998–December 2003	Date of birth: January 1998–December 2000 (hospital); January 2001 forward (birth certificates)	226,291	939	596	63.5
California	8 Counties	October 1997–December 2003	Hospital records	365,043	937	686	73.2
Georgia	5 Counties: metropolitan Atlanta	October 1997–December 2003	Date of birth: January 1997–December 1999 (hospital), January–December 2000 (mixed), January 2001 forward (birth certificates)	367,515	854	530	62.1
Iowa	Statewide	October 1997–December 2003	Birth certificates	226,365	887	551	62.1
Massachusetts	Statewide ^e	October 1997–December 2003	Birth certificates	411,955	963	642	66.7
New Jersey	Statewide	January 1998–September 2002	Birth certificates	546,544	904	579	64.0
New York	Western New York, lower Hudson valley	October 1997–December 2003	Hospital records	297,420	743	462	62.2
North Carolina	19 Counties	January 2003–December 2003	Birth certificates	40,826	255	167	65.5
Texas	West Texas and Panhandle health service areas ^f	October 1997–December 2003	Hospital records	483,448	917	618	67.4
Utah	Statewide	January 2003–December 2003	Birth certificates	49,834	186	143	76.9
Total				3,015,241	7,585	4,974	65.6
Total analytic sample	Excludes New Jersey			2,468,697	6,681	4,395	65.8

Abbreviation: EDD, estimated date of delivery.

^a Hospital records: stratified random selection of controls from hospital records by month and birth hospital weighted by the number of births per hospital per year; birth certificates: random selection from electronic birth certificates based on the EDD; mixed: selection from both hospital records and birth certificates.

^b Live infants born to mothers who were residents of the specified geographic area during the time period of participation.

^c Live infants without major birth defects born to mothers who were residents of the base population, were selected, and were eligible to participate in the study.

^d Live infants from the subset of selected controls whose mothers agreed to participate in the study and met additional inclusion criteria.

^e EDD October 1, 1997–August 31, 1998, statewide except 5 western and central counties (8 towns included that were not in this area and 3 towns excluded that were in this area); EDD September 1, 1998–December 31, 1999, statewide; EDD January 1, 2000, forward, statewide except 5 western and central counties.

^f EDD October 1, 1997–June 30, 1998, statewide except the Houston area; EDD July 1, 1998–December 31, 2001, San Antonio area, western Texas, Panhandle area; EDD January 1, 2002–December 31, 2003, western Texas, Panhandle area.

participants. The base population is defined as live infants born to mothers who were residents of the specified geographic area during the time that the center participated in NBDPS (Table 1). Selected controls were live infants without major birth defects born to mothers who were residents of the base population, were selected, and were eligible to participate in NBDPS. Control participants were the subset of selected controls whose mothers agreed to participate and met additional inclusion criteria described previously. The overall analyses for this study included birth certificate data on 2,468,697 infants and their families from base populations for the 9 centers, 6,681 selected controls, and 4,395 participant controls (Table 1).

Natality data tabulated for each of these 3 groups included maternal age at birth, race/ethnic group, education, previous livebirths, prenatal care entry, smoking during pregnancy, diabetes, and paternal age, as well as infant birth weight, gestational age, and plurality. Paternal age is missing on a significant percentage of birth certificates (about 13%). California was excluded from analyses of maternal smoking because that state did not record these data on birth certificates.

Tabulated data from each center were sent to the Centers for Disease Control and Prevention (Atlanta, Georgia) and were entered into separate Excel spreadsheets (Microsoft Corporation, Redmond, Washington, 2003) for the base population, the selected controls, and the control participants. Excel was used to sum the data across centers for each characteristic and to calculate the total number of infants with each characteristic (e.g., participant mothers aged <20 years).

Natality data on livebirths for the total US population from October 1997 to December 2003 were compiled and tabulated by scientific staff at the National Center for Health Statistics (Hyattsville, Maryland) for the variables specified above. In addition, National Center for Health Statistics staff compiled and tabulated data for each state included in NBDPS for the study time period (data not shown).

We compared the distributions of characteristics of control participants with those of 1) selected, but nonparticipant, controls; 2) the base population (excluding control participants); and 3) the US population (excluding control participants). We also compared the distribution of characteristics of selected controls and control participants with those of their base populations separated by the center's control selection procedure (hospital records vs. electronic birth certificates). Hospital controls included infants born in NBDPS geographic areas of California, New York, and Texas, as well as Georgia from October 1997 to December 1999 and Arkansas from January 1998 to December 2000. Birth certificate controls included infants born in NBDPS geographic areas of Iowa, Massachusetts, North Carolina, New Jersey, and Utah, as well as Georgia from January 2001 to December 2003 and Arkansas from January 2001 to December 2003. Birth certificate data for infants in Georgia from January 2000 to December 2000 were excluded from stratified analyses because controls were selected from either birth certificates or hospital records.

We used chi-square tests to compare overall differences in distributions of the selected characteristic (e.g., maternal

age) for control participants versus control nonparticipants. We also calculated the selection probability from the base population (S_{Bj}) for the selected controls and control participants at each exposure level (j). (For a dichotomous exposure, $j = 1$ for the exposed and $j = 0$ for the unexposed.) The selection probability for control mothers aged <20 years, for example, equals the number of control mothers aged <20 years divided by the number of mothers aged <20 years in the base population (12). We then calculated selection probability ratios (SPRs) and their 95% confidence intervals for each exposure group compared with a referent (S_{Bj}/S_{B0}) (10). The SPR indicates the probability of selection and/or participation in a given group compared with the referent.

Because of the large sample size, small differences between the controls and base population are likely to be statistically significant. Thus, we also noted SPR <0.80 or SPR >1.25 and absolute differences of >5 percentage points.

RESULTS

The number of selected controls ($n = 6,681$) represented 2.7 per 1,000 infants in the base population (Table 1). Of the selected controls in our sample, 65.8% (62.1%–76.9% by center) participated in NBDPS (i.e., were control participants).

Selected controls versus the base population

NBDPS-selected controls differed statistically from the base population regarding maternal race/ethnicity, paternal age, maternal smoking, infant birth weight, gestational age, and plurality but not maternal age or education, previous livebirths, trimester during which prenatal care began, or diabetes (Table 2). Relative differences in maternal race/ethnicity, maternal smoking, and paternal age were 0.80–1.25, and absolute differences were <5 percentage points.

Compared with their base populations, selected controls were less likely to weigh 500–1,499 or 1,500–2,499 versus $\geq 2,500$ g at birth (SPR = 0.54 and SPR = 0.88, respectively), were less likely to be born at 20–32.9 or 33–36 vs. ≥ 37 weeks' gestation (SPR = 0.65 and SPR = 0.86, respectively), and were less likely to be triplets or more or twins versus singletons (SPR = 0.39 and SPR = 0.72, respectively). The largest absolute difference was 1.6 percentage points (92.1% of selected controls vs. 90.5% of their base populations were born at ≥ 37 weeks' gestation).

Control participants versus the base population

Similar to selected controls, NBDPS control participants differed from their base population regarding maternal race/ethnicity, infant birth weight, gestational age at birth, and plurality. Mothers of control participants were less likely to be non-Hispanic black, Hispanic, Asian/Pacific Islander, or other race/ethnicity versus non-Hispanic white (SPR = 0.86, SPR = 0.78, SPR = 0.59, and SPR = 0.71, respectively). The absolute difference between control participants and their base population regarding the proportion of non-Hispanic

white mothers was 5.8 percentage points (62.2% of control participants vs. 56.4% of their base population). The largest absolute difference in infant characteristics was in the proportion of infants born at ≥ 37 weeks' gestation (91.8% of control participants vs. 90.5% of their base populations, an absolute difference of 1.3 percentage points).

Mothers of control participants also were less likely than mothers in the base population to have less than a high school education or a high school education or to have a general equivalency diploma versus more than a high school education (SPR = 0.73 and SPR = 0.88, respectively), and they were less likely to begin prenatal care in the second trimester or in the third trimester or not at all versus in the first trimester (SPR = 0.85 and SPR = 0.69, respectively). Absolute differences in these characteristics were ≤ 5 percentage points. Control participants did not differ from their base population in the distributions of other characteristics shown in Table 2.

Control participants versus control nonparticipants

Among selected controls, participants differed statistically from nonparticipants regarding all selected characteristics except maternal diabetes, infant birth weight, gestational age at birth, and plurality (Table 3). Compared with selected, but nonparticipant, controls, a greater proportion of mothers of control participants were white non-Hispanic (62.2% of participants vs. 52.4% of nonparticipants), were aged ≥ 30 years (38.7% vs. 31.9%), had completed more than a high school education (52.5% vs. 36.1%), and had started prenatal care in the first trimester (84.6% vs. 77.1%) ($P < 0.001$ for all). In addition, a smaller proportion of participant mothers had more than 3 previous livebirths (3.2% vs. 4.6%, $P < 0.020$) or reported that they smoked during pregnancy (9.5% vs. 13.3%, $P < 0.001$). Almost all of these differences were > 5 percentage points, except the difference in previous livebirths.

Birth certificate controls and hospital controls

Among centers that selected controls from birth certificates, the control participation rate was 64% (Web Table 1) (This information is described in the first of 3 supplementary tables; each is referred to as "Web table" in the text and is posted on the *Journal's* website (<http://aje.oupjournals.org/>)); among centers that selected controls from hospitals, the control participation rate was 67% (Web Table 2). Notable differences and similarities regarding the results for the total NBDPS sample are described below.

Birth certificate controls versus their base population

Unlike the total NBDPS sample, in centers that selected birth certificate controls, selected controls differed statistically from their base population on maternal age and education (Web Table 1), but relative differences were 0.80–1.25 and absolute differences were < 5 percentage points. Similar to the total NBDPS sample, control participants did not differ from their base populations in terms of maternal age but did differ on maternal race/ethnicity, education, and trimester that prenatal care began.

Among centers that selected controls from birth certificates, selected controls and control participants did not differ from their base population on overall distributions of infant birth weight, gestational age, and plurality. Some differences in specific categories of infant characteristics are noted. Compared with births in their base population, at centers that selected birth certificate controls, selected controls and control participants were less likely to weigh 500–1,499 or 1,500–2,499 versus $\geq 2,500$ g (SPR = 0.68 and SPR = 0.69, respectively). Selected controls, but not control participants, were less likely to be born at 20–32.9 versus ≥ 37 weeks' gestation (SPR = 0.73) (Web Table 1). Absolute differences in infant characteristics were ≤ 0.7 percentage points.

Hospital controls versus their base population

Similar to the total NBDPS sample, in centers that selected controls from hospital records (Web Table 2), selected controls differed from their base population regarding infant characteristics. Compared with their base populations, selected (hospital) controls were less likely to weigh 500–1,499 or 1,500–2,499 g at birth versus $\geq 2,500$ g (SPR = 0.37 and SPR = 0.76, respectively), were less likely to be born at 20–32.9 or 33–36 versus ≥ 37 weeks' gestation (SPR = 0.54 and SPR = 0.77, respectively), and were less likely to be triplets or more or twins versus singletons (SPR = 0.19 and SPR = 0.49, respectively). The 95% confidence interval for triplets or more included 1. The largest absolute difference in infant characteristics (2.6 percentage points) was in the proportion of infants born at ≥ 37 weeks' gestation.

NBDPS controls versus US livebirths

Differences in the distributions of characteristics between NBDPS control participants and US livebirths were almost all statistically significant but did not appear to vary in magnitude from those between NBDPS control participants and their base population, with a few exceptions (Web Table 3). NBDPS controls did not differ from other US livebirths regarding the proportion of mothers who were Hispanic (SPR = 1.03, 95% confidence interval: 0.96, 1.11). The largest absolute difference in the distributions of characteristics between groups was 6.8 percentage points (40.1% of mothers of US livebirths vs. 46.9% of mothers of control participants had no previous livebirths).

Additional analyses

New Jersey contributed 12% of the data to the NBDPS 1997–2003 analytic sample for both selected controls and control participants. The addition of New Jersey's data did not change how well NBDPS-selected controls and control participants represented their 1997–2003 base populations in terms of maternal age or infant characteristics.

DISCUSSION

Our analysis suggests that 1997–2003 NBDPS control participants generally represent their base populations in

Table 2. Distributions and Selection Probability Ratios of Sociodemographic and Other Characteristics for All Selected Controls and Control Participants in the National Birth Defects Prevention Study^a Compared With Their Base Population, United States, October 1997–December 2003

Characteristic	Base Population (<i>n</i> = 2,468,697) ^{b,c} %	Selected Controls (<i>n</i> = 6,681) ^{b,d}			Control Participants (<i>n</i> = 4,395) ^{b,e}		
		%	Selection Probability Ratio ^f	95% Confidence Interval	%	Selection Probability Ratio ^f	95% Confidence Interval
Maternal race/ethnicity							
White, non-Hispanic	56.4	58.8	1.00		62.2	1.00	
Black, non-Hispanic	12.6	13.5	1.03	0.96, 1.10	12.0	0.86	0.79, 0.95
Hispanic	26.3	23.5	0.85	0.81, 0.91	22.6	0.78	0.72, 0.83
Asian/Pacific Islander	3.5	3.1	0.85	0.74, 0.99	2.3	0.59	0.48, 0.72
Other	1.2	1.1	0.86	0.68, 1.08	1.0	0.71	0.52, 0.96
Maternal age, years							
<20	11.8	12.6	1.05	0.96, 1.14	11.7	1.04	0.93, 1.15
20–24	24.4	24.9	1.00		23.2	1.00	
25–29	26.2	26.1	0.97	0.91, 1.04	26.4	1.06	0.98, 1.16
≥30	37.6	36.4	0.95	0.89, 1.01	38.7	1.08	1.00, 1.17
Paternal age, years ⁹							
<20	4.3	4.6	1.12	0.99, 1.27	4.2	1.00	0.85, 1.17
20–24	17.3	18.8	1.14	1.07, 1.22	17.3	1.02	0.93, 1.11
25–29	24.8	25.6	1.08	1.02, 1.15	25.6	1.04	0.97, 1.13
≥30	53.6	51.1	1.00		52.9	1.00	
Maternal education							
<High school	22.6	22.3	1.00	0.94, 1.07	18.3	0.73	0.68, 0.80
High school or general equivalency diploma	29.9	30.8	1.04	0.99, 1.10	29.2	0.88	0.82, 0.95
>High school	47.5	46.9	1.00		52.5	1.00	
Previous livebirths							
None	47.1	46.8	1.00		46.9	1.00	
1–3	49.3	49.6	1.01	0.96, 1.06	49.9	1.02	0.96, 1.08
>3	3.7	3.7	1.00	0.88, 1.14	3.2	0.87	0.73, 1.03
Trimester that prenatal care began							
First	81.8	82.1	1.00		84.6	1.00	
Second	14.1	14.0	0.99	0.93, 1.06	12.5	0.85	0.78, 0.94
Third or no prenatal care	4.1	3.9	0.95	0.84, 1.08	2.9	0.69	0.58, 0.83

Table continues

relation to paternal age and the majority of maternal sociodemographic characteristics examined, including those associated with birth defects, such as maternal age, maternal smoking status, and maternal diabetes (13–17). NBDPS control participants did differ slightly from their base populations in the distributions of maternal race/ethnicity, education, and the trimester that prenatal care began. In addition, relative, but not absolute, differences in infant low birth weight, gestational age, and plurality were notable. Our results also indicate that the magnitude and direction of the differences in sociodemographic characteristics between NBDPS control participants and the US livebirths were similar to those between control participants and their base populations.

Although the relative differences in maternal characteristics noted above were significant, only the absolute differ-

ence in the distribution of maternal race/ethnicity between control participants and their base population was greater than 5 percentage points. Previous studies also indicate that, in race/ethnic groups other than white non-Hispanic, mothers with less education and mothers with late or no prenatal care are less likely to participate in cross-sectional surveys and case-control studies (18, 19). NBDPS interviews are available in English and Spanish only. Mothers who do not speak either of these languages are excluded from participation. This factor could explain differences in the participation of groups such as Asian/Pacific Islanders, particularly in California and New York. NBDPS control participants may underrepresent these groups.

Our results suggest that differences in maternal characteristics between the base population and control participants were associated with participation rather than

Table 2. Continued

Characteristic	Base Population (<i>n</i> = 2,468,697) ^{b,c} %	Selected Controls (<i>n</i> = 6,681) ^{b,d}			Control Participants (<i>n</i> = 4,395) ^{b,e}		
		%	Selection Probability Ratio ^f	95% Confidence Interval	%	Selection Probability Ratio ^f	95% Confidence Interval
Maternal smoking during pregnancy ^h							
No	90.1	89.1	1.00		90.5	1.00	
Yes	9.9	10.9	1.11	1.02, 1.20	9.5	0.96	0.86, 1.07
Maternal diabetes							
Yes (any)	2.8	2.6	0.93	0.80, 1.07	2.7	0.95	0.79, 1.15
No (none)	97.2	97.4	1.00		97.3	1.00	
Infant birth weight, g							
500–1,499	1.3	0.68	0.54	0.40, 0.72	0.7	0.58	0.41, 0.85
1,500–2,499	6.0	5.4	0.88	0.79, 0.98	5.2	0.85	0.74, 0.97
≥2,500	92.7	93.9	1.00		94.0	1.00	
Infant gestational age, weeks							
20–32.9	2.2	1.5	0.65	0.53, 0.80	1.6	0.72	0.56, 0.91
33–36	7.3	6.4	0.86	0.78, 0.95	6.6	0.89	0.79, 1.01
≥37	90.5	92.1	1.00		91.8	1.00	
Plurality							
Singleton	96.8	97.7	1.00		97.6	1.00	
Twin	3.0	2.2	0.72	0.61, 0.85	2.3	0.76	0.63, 0.93
≥Triplets	0.2	0.1	0.39	0.16, 0.94	0.1	0.59	0.25, 1.42

^a Includes data from Arkansas, California, Georgia, Iowa, Massachusetts, New York, North Carolina, and Utah.

^b The denominators for each variable do not add to the totals because of different amounts of underreported or missing birth certificate data. For most variables, the percentage of missing data is less than 4% (e.g., *n* = 66 for plurality to *n* = 83,896 for trimester that prenatal care began for the base population), except for paternal age and maternal smoking during pregnancy (refer to the footnotes for these variables).

^c Live infants born to mothers who were residents of the specified geographic area during the time period of participation.

^d Live infants without major birth defects born to mothers who were residents of the base population, were selected, and were eligible to participate in the study.

^e Live infants from the subset of selected controls whose mothers agreed to participate in the study and met additional inclusion criteria.

^f Probability of selection in a given group compared with the referent; that is, S_{Bj}/S_{B0} , where, for example, S_{B0} = number of participants whose mothers were white non-Hispanic ÷ number of infants in the base population whose mothers were white non-Hispanic and S_{Bj} = number of participants whose mothers were black non-Hispanic ÷ number of infants in the base population whose mothers were black non-Hispanic. Selection probability ratios are unadjusted.

^g For about 13% (*n* = 315,014) of the base population, 13% (*n* = 886) of selected controls, and 11% (*n* = 482) of control participants, data on paternal age are missing because of underreported or missing birth certificate data.

^h For about 18% (*n* = 374,703) of the base population, 14% (*n* = 963) of selected controls, and 16% (*n* = 705) of control participants, data on maternal smoking during pregnancy are missing. Most of the missing data on maternal smoking during pregnancy are from California (*n* = 365,043 for the base population, *n* = 937 for selected controls, and *n* = 686 for control participants). California did not report data on maternal smoking during pregnancy on birth certificates during the reporting period. Comparisons of the distributions of maternal smoking during pregnancy exclude California.

selection. Relative and absolute differences between the base population and selected controls were small. Except for Texas and New York, the magnitude and direction of results did not differ by center. In Texas, compared with the base population, selected controls were less likely to be Asian/Pacific Islander (SPR = 0.31, 95% confidence interval: 0.12, 0.83). In New York, compared with the base population, selected controls were more likely to be black/non-Hispanic or Hispanic (SPR = 1.37, 95% confidence interval: 1.13, 1.67 and SPR = 1.29, 95% confidence interval: 1.01, 1.64), respectively) and less likely to be Asian/Pacific Islander (SPR = 0.58, 95% confidence interval: 0.34, 0.99). Absolute differences were <5 percentage points.

Our results suggest that center selection method rather than participation resulted in the lower proportion of control participants who were low birth weight, preterm, and/or multiples. The magnitude of and direction of results did not differ by center. Similar to previous studies, participation did not differ by infant low birth weight, preterm delivery, or plurality (19, 20). A possible explanation for this finding is that the stratified sampling of hospitals by number of births per year does not capture the variation in infant characteristics between hospitals (e.g., risk of low birth weight may not be a factor of the number of infant births per year per hospital) and results in a less representative sample of control infants. This possibility was suggested

Table 3. Distributions of Characteristics by Participation Status of Selected Controls,^a National Birth Defects Prevention Study,^b United States, October 1997–December 2003

Characteristic	Control Participants ^c (n = 4,395)		Control Nonparticipants ^c (n = 2,286)		χ^2 P Value (Control Participants vs. Nonparticipants)
	No.	%	No.	%	
Maternal race/ethnicity					<0.001
White, non-Hispanic	2,720	62.2	1,195	52.4	
Black, non-Hispanic	525	12.0	374	16.4	
Hispanic	988	22.6	574	25.2	
Asian/Pacific Islander	99	2.3	107	4.7	
Other	42	1.0	31	1.4	
Maternal age, years					<0.001
<20	511	11.7	331	14.5	
20–24	1,015	23.2	645	28.3	
25–29	1,159	26.4	579	25.3	
≥30	1,697	38.7	728	31.9	
Paternal age, years ^d					<0.001
<20	166	4.2	100	5.3	
20–24	678	17.3	411	21.8	
25–29	1,000	25.6	481	25.6	
≥30	2,069	52.9	890	47.3	
Maternal education					<0.001
<High school	792	18.3	675	30.1	
High school or general equivalency diploma	1,265	29.2	760	33.9	
>High school	2,271	52.5	810	36.1	
Previous livebirths					0.020
None	2,027	46.9	1,052	46.5	
1–3	2,157	49.9	1,108	49.0	
>3	138	3.2	103	4.6	
Trimester that prenatal care began					<0.001
First	3,602	84.6	1,701	77.1	
Second	530	12.5	376	17.1	
Third or no prenatal care	125	2.9	128	5.8	

Table continues

in previous studies as a potential problem with hospital-based control selection in general (1, 3). Because of differences in referral and delivery practices for very preterm or low birth weight infants (the majority of whom are delivered at tertiary or teaching hospitals), these births are not uniformly distributed among the hospitals within a given catchment area. This factor could explain why these neonates are underrepresented in the selected samples among centers with hospital-based sampling.

Strengths of this study include the large sample size as well as the comparison of several maternal sociodemographic and behavioral and infant health characteristics. We examined whether selection or participation was responsible for differences between controls and their base populations. Finally, we stratified centers by selection method to compare differences in representativeness by center selection method: hospital versus birth certificates.

Our findings are subject to potential limitations. The use of birth certificate data limited us to characteristics consistently collected across states. Observed differences in maternal smoking may not apply to California, where these data were not collected. Results for paternal age and diabetes may need to be interpreted with caution because of missing or underreported information (21). Observed findings regarding some characteristics may not apply to New Jersey. Two centers (Utah and North Carolina) provided only 1 year of data; thus, representativeness may change as the contribution of these centers to the overall NBDPS sample increases.

Only aggregate data were provided by centers and analyzed, so we were unable to examine combinations of characteristics. In addition, the lack of individual data did not enable us to examine whether the differences in continuous variables (e.g., birth weight) were due to shifts in the

Table 3. Continued

Characteristic	Control Participants ^c (n = 4,395)		Control Nonparticipants ^c (n = 2,286)		χ^2 P Value (Control Participants vs. Nonparticipants)
	No.	%	No.	%	
Maternal smoking during pregnancy ^a					<0.001
No	3,338	90.5	1,759	86.7	
Yes	352	9.5	269	13.3	
Maternal diabetes					0.636
Yes (any)	118	2.7	57	2.5	
No (none)	4,256	97.3	2,221	97.5	
Infant birth weight, g					0.586
500–1,499	32	0.7	13	0.6	
1,500–2,499	227	5.2	127	5.7	
$\geq 2,500$	4,079	94.0	2,100	93.8	
Infant gestational age, weeks					0.246
20–32.9	69	1.6	27	1.2	
33–36	282	6.6	133	6.0	
≥ 37	3,920	91.8	2,075	92.8	
Plurality					0.195
Singleton	4,279	97.5	2,234	98.0	
Twin	102	2.3	46	2.0	
\geq Triplets	5	0.1	0	0.0	

^a Selected controls: live infants without major birth defects born to mothers who were residents of the base population, were selected, and were eligible to participate in the study; control participants: live infants from the subset of selected controls whose mothers agreed to participate in the study and met additional inclusion criteria.

^b Includes data from Arkansas, California, Georgia, Iowa, Massachusetts, New York, North Carolina, and Utah.

^c The denominators for each variable do not add to the totals because of different amounts of underreported or missing birth certificate data. For most variables, the percentage of missing data is less than 4% (e.g., $n = 9$ for plurality to $n = 138$ for trimester that prenatal care began among selected controls), except for paternal age and maternal smoking during pregnancy (refer to the footnotes for these variables).

^d Paternal age information is missing from birth certificates for 11% ($n = 482$) of control participants and 18% ($n = 404$) of control nonparticipants.

^e About 16% ($n = 705$) of control participants and 11% ($n = 258$) of control nonparticipants are missing birth certificate data on maternal smoking during pregnancy. Most of the missing data on maternal smoking during pregnancy is from California ($n = 686$ for the control participants and $n = 251$ for the control nonparticipants). California did not report data on maternal smoking during pregnancy on birth certificates during the reporting period. Comparisons of the distributions of maternal smoking during pregnancy exclude California.

distribution or differences in the variance. Some of the cells had a limited sample size. Although we believe that the differences in the distributions of infant low birth weight, preterm delivery, and multiple birth between NBDPS controls and the base populations occurred primarily in the centers that selected controls from birth hospitals, we cannot say definitively that selection method is responsible for this difference because we were unable to compare the 2 selection methods within the same base population.

In epidemiologic studies, both selection method and participation can bias the associations between exposure and outcome if the association between the exposure and outcome among those selected for analysis differs from the association among those eligible (1). To the extent that NBDPS control participants do not represent the base or US population, the estimates of the exposure prevalence,

attributable fraction, or distribution based on analyses of controls should be interpreted with caution, particularly if the exposure of interest is strongly associated with maternal race/ethnicity, education, or entry to prenatal care or with infant birth weight, gestational age, or multiple births.

Selection of population controls from the same base population as cases presents a major methodological advantage in NBDPS (1, 3). To the extent that NBDPS case and control participants represent the population base and that procedures for recruitment and ascertainment of information are identical, the likelihood of bias due to selection or participation of controls in this study is reduced. Participation rates (number interviewed/number eligible and included) do not differ substantially for cases and controls: 70.5% and 67.2%, respectively. (Participation rates are slightly higher than the percentage of participants among selected controls

because the denominators for participation rates exclude ineligible controls.) NBDPS centers attempt to capture 100% of the birth defects under study within their base populations. To the extent that this goal is achieved, the probability of case selection should not vary by infant or other characteristics. Although it is difficult to evaluate the actual proportion of cases ascertained, most of the defects chosen for inclusion in NBDPS were those that are apparent and could be accurately identified by 6 weeks of age, although some cases can be identified after 1 year of age. Investigation of completeness of case ascertainment and case participation by sociodemographic and infant characteristics would allow for an evaluation of and potential correction factors for selection bias in subsequent studies.

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