



Practice of Epidemiology

Adjusting for Bias Due to Incomplete Case Ascertainment in Case-Control Studies of Birth Defects

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Case-control studies of birth defects might be subject to selection bias when there is incomplete ascertainment of cases among pregnancies that are terminated after a prenatal diagnosis of the defect. We propose a simple method to estimate inverse probability of selection weights (IPSWs) for cases ascertained from both pregnancies that end in termination and those that do not end in termination using data directly available from the National Birth Defects Prevention Study and other published information. The IPSWs can then be used to adjust for selection bias analytically. We can also allow for uncertainty in the selection probabilities through probabilistic bias analysis. We provide an illustrative example using data from National Birth Defects Prevention Study (1997–2009) to examine the association between prepregnancy obesity (body mass index, measured as weight in kilograms divided by height in meters squared, of ≥ 30 vs. < 30) and spina bifida. The unadjusted odds ratio for the association between prepregnancy obesity and spina bifida was 1.48 (95% confidence interval: 1.26, 1.73), and the simple selection bias-adjusted odds ratio was 1.26 (95% confidence interval: 1.04, 1.53). The probabilistic bias analysis resulted in a median adjusted odds ratio of 1.22 (95% simulation interval: 0.97, 1.47). The proposed method provides a quantitative estimate of the IPSWs and the bias introduced by incomplete ascertainment of cases among terminated pregnancies conditional on a set of assumptions.

bias correction; birth defects; case-control studies; selection bias; spina bifida

Abbreviations: BMI, body mass index; DAG, directed acyclic graph; IPSW, inverse probability of survival weights; NBDPS, National Birth Defects Prevention Study.

Selection bias is a concern in studies of birth defects. Several potential mechanisms have been posited (1–4), including bias due to incomplete ascertainment of cases among terminated pregnancies (5–13). Because ascertainment of terminated pregnancies is more difficult than ascertainment of live births and stillbirths, selection bias can occur when a prenatal diagnosis of a birth defect increases the probability of termination and the probability of termination differs by exposure status (6, 9). For example, some birth defects might be more difficult to visualize using prenatal ultrasound in women with a higher body mass index (BMI) (14, 15). Therefore, obese women could be less likely to receive a prenatal diagnosis and consequently less likely to consider terminating an

affected pregnancy. Thus, in a study of prepregnancy obesity and birth defects, both the exposure and the outcome could affect selection, potentially resulting in selection bias. Generally, the extent of case underascertainment in studies of birth defects is unknown and likely varies widely by setting and ascertainment method (13, 16–18).

Although investigators have previously proposed formulas to address incomplete case ascertainment in birth defect studies (5, 6), we were unable to find studies in which these approaches were implemented. This is likely due to the challenge of identifying sufficient information to estimate the required exposure-specific selection probabilities (19). We proposed a method to estimate inverse probability of selection weights (IPSWs) to

adjust for selection bias arising from incomplete ascertainment of cases. We estimated IPSWs and bias-adjusted odds ratios using data from the National Birth Defects Prevention Study (NBDPS).

MOTIVATING EXAMPLE

Associations between prepregnancy obesity and spina bifida in offspring have consistently been found in epidemiologic studies (11, 20). However, it has been posited that these associations might be explained by selection bias resulting from incomplete ascertainment of cases among pregnancies that ended in termination (10–12).

In Figure 1, we illustrate the disposition of fetuses with spina bifida to cases in which a fetus can receive prenatal testing or not, and if tested, spina bifida can be diagnosed or not. Each pregnancy could end in spontaneous abortion, termination, live birth, or stillbirth. In most studies of birth defects, spontaneous abortions are excluded because they are difficult to identify, particularly at early gestational ages, and the presence or absence of a birth defect is often unknown. For these reasons, we excluded them from our analysis. A prenatal diagnosis of a birth defect can lead to termination of a pregnancy, or termination can occur for reasons unrelated to prenatal diagnosis (among untested pregnancies and those with a false-negative result). Our approach corrects for incomplete ascertainment of both types of terminations. We excluded pregnancies that were terminated before 13 weeks of gestation, which is approximately the earliest gestational age at which spina bifida could be prenatally diagnosed (21), because most epidemiologic studies do not ascertain these cases. We assumed that the number of terminated pregnancies at 13 gestational weeks and older were incompletely ascertained. For simplicity, we assumed complete ascertainment of pregnancies ending in live births or stillbirths. Our approach could address incomplete ascertainment of liveborn and stillborn cases, but for spina bifida, case ascertainment of live births and stillbirths is thought to be high (22). Thus, for this example, the cases included all live births and stillbirths with spina bifida and a subset of pregnancies affected by spina bifida that were terminated at a gestational age of 13 weeks or later.

Although underascertainment of cases can occur in a cohort study or a case-control study, for birth defect studies, the case-control design is more feasible (and more common) because birth defects are relatively rare outcomes (17). In our example, controls were a random sample of live births with no major birth defects, which is consistent with the design of many birth defect studies (23–25).

In the directed acyclic graph (DAG) in Figure 2A, we hypothesized that prepregnancy obesity affects spina bifida, that having spina bifida affects whether or not spina bifida is prenatally diagnosed, and that a prenatal diagnosis affects whether a pregnancy is terminated. Further, prepregnancy obesity affects whether a fetus is prenatally diagnosed because it can impair ultrasound visualization of spina bifida. In a case-control study, the outcome affects selection into the study. Pregnancy termination also affects selection into the study because terminated pregnancies are incompletely ascertained. The effect of prepregnancy obesity on spina bifida might be

confounded by unspecified confounders (Figure 2A). In prior studies, results that were adjusted for suspected confounders differed minimally from unadjusted results (11, 12), although unidentified confounders might still have existed. For clarity, we started with an overly simplistic DAG in which we assumed no unmeasured confounders (Figure 2B). We then adjusted for selection bias in the presence of suspected confounding. For both scenarios, we assumed that the exposure, outcome, and prenatal diagnosis were not misclassified or missing.

APPROACH

Our goal was to estimate the association between prepregnancy obesity and spina bifida after adjustment for bias due to incomplete ascertainment of cases. We did this by estimating IPSWs, which we used to calculate a bias-adjusted association in a pseudopopulation with complete case ascertainment (26). Essentially, each case was weighted by the inverse of the probability that a case with those characteristics would be selected. For example, because terminated cases are less likely to be selected than are cases that are not terminated, selected terminated cases were weighted heavier than selected liveborn and stillborn cases to compensate for the missing cases. This recreated the distribution of the cases in the source population, assuming that the selected cases were representative of the unobserved cases.

To estimate IPSW, we first need to estimate selection probabilities for cases among terminated pregnancies conditional on obesity status of the woman and prenatal diagnosis status of the fetus represented as $P(S|T, Ob, Dx)$, $P(S|T, \overline{Ob}, Dx)$, $P(S|T, Ob, \overline{Dx})$, and $P(S|T, \overline{Ob}, \overline{Dx})$, where S represents selection (S indicates selected and \bar{S} indicates not selected), T represents termination of the pregnancy (T indicates terminated and \bar{T} indicates not terminated), Ob represents prepregnancy obesity (Ob indicates obese and \overline{Ob} indicates not obese), and Dx represents a prenatal diagnosis of spina bifida (Dx indicates diagnosed and \overline{Dx} indicates not diagnosed). In Figure 2B, the selection of cases is independent of prepregnancy obesity and prenatal diagnosis given termination because among cases, prepregnancy obesity only affects selection of terminated pregnancies through prenatal diagnosis, and prenatal diagnosis only affects selection through termination. Thus, the 4 selection probabilities can be simplified to the common probability $P(S|T)$. Similarly, selection of cases is independent of prepregnancy obesity and prenatal diagnosis given no termination of pregnancy and can be simplified to $P(S|\bar{T})$. Thus, given our assumptions, we need only 2 IPSW, which are conditional on whether the pregnancy was terminated or not and which can be calculated as follows.

First, we assume that the likelihood of pregnancy termination for cases is independent of prepregnancy obesity given prenatal diagnosis (Figure 2B), as follows:

$$P(T|Dx, Ob) = P(T|Dx, \overline{Ob}) = P(T|Dx)$$

and

$$P(T|\overline{Dx}, Ob) = P(T|\overline{Dx}, \overline{Ob}) = P(T|\overline{Dx}).$$

Given our assumptions, we can estimate $P(Dx|Ob)$ using the following equation:

$$P(Dx|Ob) = \frac{P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]}{[1 - P(T|Dx)][1 - P(Dx|\bar{T}, Ob, S)] + P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]} \tag{1}$$

A detailed proof is provided in Appendix 1. Similarly, $P(Dx|\overline{Ob})$ can be estimated using the following equation:

$$P(Dx|\overline{Ob}) = \frac{P(Dx|\bar{T}, \overline{Ob}, S)[1 - P(T|\bar{Dx})]}{[1 - P(T|Dx)][1 - P(Dx|\bar{T}, \overline{Ob}, S)] + P(Dx|\bar{T}, \overline{Ob}, S)[1 - P(T|\bar{Dx})]} \tag{2}$$

Only 3 probability estimates are needed for each equation: 1) the probability of prenatal diagnosis among pregnancies in the study that were not terminated conditional on prepregnancy obesity status ($P(Dx|\bar{T}, Ob, S)$ or $P(Dx|\bar{T}, \overline{Ob}, S)$), 2) the probability of termination given a prenatal diagnosis ($P(T|Dx)$), and 3) the probability of termination given no prenatal diagnosis ($P(T|\bar{Dx})$). These probabilities can be estimated from study data, if available, or the literature.

The next step is to use these values to estimate $P(S|T)$ using the following equation:

$$P(S|T) = \frac{\frac{M_1}{P(Dx|Ob)P(T|Dx)} + \frac{M_2}{P(Dx|\overline{Ob})P(T|Dx)}}{\frac{Q_1}{P(S|\bar{T})[1 - P(T|\bar{Dx}) + P(Dx|Ob)P(T|\bar{Dx}) - P(Dx|Ob)P(T|Dx)]} + \frac{Q_2}{P(S|\bar{T})[1 - P(T|\bar{Dx}) + P(Dx|\overline{Ob})P(T|\bar{Dx}) - P(Dx|\overline{Ob})P(T|Dx)]}} \tag{3}$$

where M_1 is the number of obese cases selected into the study with T and Dx , M_2 is the number of nonobese cases selected into the study with T and Dx , Q_1 is the number of obese cases selected into the study with \bar{T} , and Q_2 is the number of nonobese cases selected into the study with \bar{T} . These values can be determined directly from study data if available. The proof of this equation is provided in Appendix 2.

The estimated IPSW for cases among terminated pregnancies is $w_T = 1/P(S|T)$. The estimated IPSW for liveborn and stillborn cases is $w_{\bar{T}} = 1/P(S|\bar{T})$, which can be estimated from the literature or from study participation rates. Under our assumption of complete ascertainment of live births and stillbirths, $P(S|\bar{T}) = 1$.

The IPSW can be used to adjust for selection bias by hand or using modeling software (26). Each case ascertained among terminated pregnancies is assigned $IPSW = 1/P(S|T)$, and each liveborn or stillborn case is assigned the $IPSW = 1/P(S|\bar{T})$, which equals 1 in this example. All controls are assigned $IPSW = 1$ under the assumption that the distribution of prepregnancy obesity in the controls represents the distribution in the source population. To estimate standard errors and confidence intervals, a robust variance estimator must be used to take into account the inflation of the sample size that is introduced by weighting; for example, in SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina), PROC GENMOD could be used with the REPEATED statement (Web Appendix 1, available at <http://aje.oxfordjournals.org>). In the presence of confounding, separate IPSWs for each stratum of the confounder are required. These confounder-specific weights are applied in a model that includes the confounder as an independent variable.

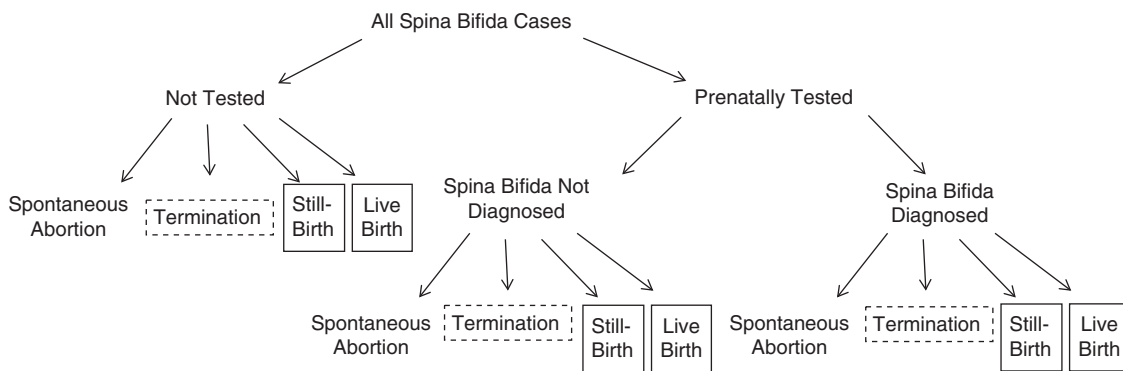


Figure 1. The possible outcomes of all pregnancies in which spina bifida is present are illustrated. Each pregnant woman receives prenatal testing or not, and if tested, spina bifida is prenatally diagnosed or not. Four outcomes are possible for each pregnancy: spontaneous abortion, termination of pregnancy, live birth, or stillbirth. We assume complete ascertainment of live and stillbirths (boxes with solid outline); incomplete ascertainment of terminations at or after 13 weeks' gestation and no ascertainment of terminations before 13 weeks' gestation (boxes with dashed outline); and no ascertainment of spontaneous abortions.

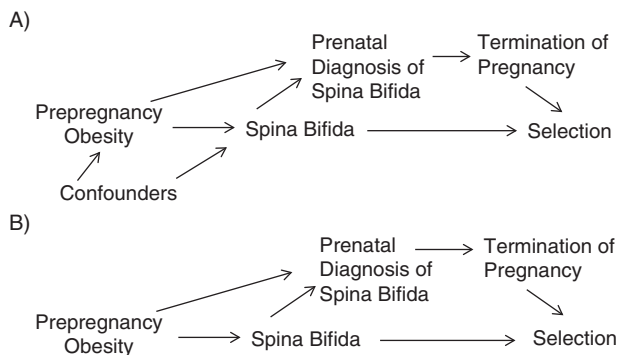


Figure 2. A) In this directed acyclic graph, we examine the effect of prepregnancy obesity on spina bifida in pregnancies surviving to 13 weeks' gestation. There might be confounders of this association (e.g., race/ethnicity). Having spina bifida affects the likelihood of prenatal diagnosis, and prepregnancy obesity affects whether spina bifida is diagnosed prenatally. Having a prenatal diagnosis of spina bifida affects the likelihood of termination of pregnancy. In a case-control study, spina bifida affects selection into the study. Termination also affects selection because terminated pregnancies are more difficult to ascertain. In B, we show a simplified version of A in which we assume there are no unmeasured confounders.

An Excel worksheet that calculates the IPSWs, the bias-adjusted contingency table, and the bias-adjusted odds ratio is available from the corresponding author upon request. The calculated IPSWs can then be applied in a statistical software program such as SAS to obtain the bias-adjusted 95% confidence interval.

We can allow for uncertainty in the estimates used to calculate the IPSW (e.g., $P(T|Dx)$) by performing a probabilistic bias analysis (19). First, each of the parameters is assigned a probability distribution reflecting the uncertainty about its true value. Then, we repeatedly sample from each distribution and calculate the corresponding IPSWs, which are used to estimate the bias-adjusted odds ratio. The median bias-adjusted odds ratio across all samples provides a point estimate. To calculate a 95% simulation interval, we must apply to each bias-adjusted odds ratio the formula $\exp(\log(\text{bias-adjusted OR}_i) + \text{error}_i)$, where OR is the odds ratio, $i = 1$ to the total number of samples, and error_i is drawn from $\sim N(0, s)$, where s is the standard deviation of the unadjusted odds ratio. The resulting 2.5th and 97.5th percentiles define the 95% simulation interval.

NUMERIC EXAMPLE

We illustrate this approach using data from the NBDPS, a large, multisite, population-based case-control study of risk factors for major structural birth defects. NBDPS has been described in detail previously (23). In brief, cases with 1 or more major birth defects were identified through surveillance programs, and controls (liveborn infants with no major birth defects) were identified from birth certificates or hospital records from the same catchment areas and time period as the cases. Eligible participants had estimated delivery dates from October 1, 1997, to December 31, 2009. The present analysis

was limited to participants from NBDPS sites that ascertained cases among live births, stillbirths (fetal deaths at ≥ 20 weeks' gestation), and terminated pregnancies (functionally limited to gestational ages when a prenatal diagnosis is possible). These sites included Arkansas, California, Georgia, Iowa, and Texas (1997–2009); New York (2000–2009); and North Carolina and Utah (2003–2009). Procedures for ascertaining cases among terminated pregnancies varied by study site. Ascertainment is likely incomplete at all sites, although the extent of underascertainment varies. For simplicity, we estimated average IPSWs across sites. NBDPS was approved by institutional review boards at all participating sites.

Participating women completed a computer-assisted telephone interview 6 weeks to 2 years after the estimated date of delivery. BMI was calculated using self-reported prepregnancy weight (kilograms) divided by self-reported height (meters) squared. For simplicity, in this example, study participants were classified as obese (BMI ≥ 30) or not obese (BMI < 30). Women with missing data on BMI (72 cases (7%) and 434 controls (5%)) or with unknown pregnancy outcome (4 cases and 31 controls) were excluded from this analysis. The final sample included 929 women with pregnancies affected by spina bifida (cases) and 7,774 women with unaffected pregnancies (controls).

Prenatal diagnosis of spina bifida

Information on prenatal diagnosis of spina bifida was collected during the interview from women with estimated delivery dates through December 31, 2005. After this time, the interview did not include questions about prenatal diagnosis. Women were asked if they had an abnormal ultrasound and if yes to describe the abnormality. We classified women as having reported a prenatal diagnosis if they identified spina bifida by name, provided an anatomical description consistent with spina bifida, described an anomaly that was likely to be spina bifida, or reported fetal surgery for in utero spina bifida repair. Classification of prenatal diagnosis was made by 2 reviewers who successfully resolved all differences by consensus. Classification was done with knowledge of case status to decrease false negatives due to vaguely reported ultrasound results. Women who reported diagnoses based on amniocentesis, chorionic villus sampling, serum α -fetoprotein screening, or other prenatal tests were classified as having reported a prenatal diagnosis even though these tests are not diagnostic for spina bifida. We assumed that these women did not remember that the ultrasound provided the confirmatory diagnosis.

Estimation of IPSWs

The IPSWs for the cases were estimated from data collected by NBDPS and data available in the literature (Table 1). The following information for both obese women and women who were not obese were available directly from NBDPS: 1) the number of women with pregnancies prenatally diagnosed with spina bifida that were terminated, 2) the number of women whose pregnancies were not terminated, and 3) the proportion of women in the study with a liveborn or stillborn case who reported a prenatal diagnosis. These data were assumed to apply to the full study period but were restricted to

Table 1. Information Needed to Calculate Weights to Adjust for Selection Bias Due to Incomplete Ascertainment of Cases Among Pregnancies Terminated After Prenatal Diagnosis^a

Description	Notation	Value	Source
No. of obese women in the study with pregnancies that were prenatally diagnosed with spina bifida and terminated	M_1	8	Directly observed count ^b
No. of nonobese women in the study with pregnancies that were prenatally diagnosed with spina bifida and terminated	M_2	46	Directly observed count ^b
No. of obese women in the study with pregnancies that were not terminated	Q_1	142	Directly observed count ^b
No. of nonobese women in study with pregnancies that were not terminated	Q_2	372	Directly observed count ^b
Among obese women in the study with pregnancies that were not terminated, the proportion with a prenatal diagnosis	$P(Dx \bar{T}, Ob, S)$	0.55	Calculate based on directly observed counts ^b
Among nonobese women in the study with pregnancies that were not terminated, the proportion with a prenatal diagnosis	$P(Dx \bar{T}, \bar{Ob}, S)$	0.50	Calculate based on directly observed counts ^b
Among all pregnancies affected by spina bifida that were prenatally diagnosed, the proportion that were terminated	$P(T Dx)$	0.49	Need estimate from literature
Among all pregnancies affected by spina bifida that were not prenatally diagnosed, the proportion that were terminated	$P(T \bar{Dx})$	0.03	Need estimate from literature

Table continues

women with an estimated delivery date of December 31, 2005, or earlier because only these women were asked about prenatal diagnosis in NBDPS. The fact that prenatal diagnoses of other birth defects did not increase from 2000 to 2005 provides some support for this assumption (27, 28).

The proportion of terminated pregnancies among all prenatally diagnosed pregnancies affected with spina bifida was estimated from a recent systematic review (16). The proportion of pregnancies terminated at a gestational age of 13 weeks or later among pregnancies affected with spina bifida but not prenatally diagnosed was also estimated from the literature. This value is less readily available; the derivation of our estimate is described in Web Appendix 2 (29, 30). We assumed that NBDPS had complete ascertainment of liveborn and stillborn spina bifida cases in the states included for this study, so $P(S|\bar{T}) = 1.00$ and thus IPSW = 1.

Table 1. Continued

Description	Notation	Value	Source
Among pregnancies affected by spina bifida that were not terminated, the proportion that were selected	$P(S \bar{T})$	1.00	Based on study design
Among obese women with pregnancies affected by spina bifida, the proportion of pregnancies that were prenatally diagnosed	$P(Dx Ob)$	0.70	Estimated using equation 1
Among nonobese women with pregnancies affected by spina bifida, the proportion of pregnancies that were prenatally diagnosed	$P(Dx \bar{Ob})$	0.66	Estimated using equation 2
Among all pregnancies affected by spina bifida and terminated, the proportion that were selected	$P(S T)$	0.21	Estimated from above using equation 3
Weight applied to terminated case pregnancies in the study	w_T	4.65	$1/P(S T)$
Weight applied to live birth and stillbirth cases in the study	$w_{\bar{T}}$	1.00	$1/P(S \bar{T})$

^a All data in the table were restricted to pregnancies affected by spina bifida only.

^b Based on a study population with an estimated delivery date on or before December 31, 2005, which restricts the population to women who were asked about prenatal testing. We assumed that the proportions did not change over time.

Inserting the values from Table 1 into equations 1 and 2, we estimated the proportion of pregnancies affected by spina bifida that were prenatally diagnosed among obese and nonobese women. Next, we used equation 3 to estimate the proportion of pregnancies selected into the study among terminated, affected pregnancies. The IPSW for terminated cases was the inverse of this proportion.

Adjustment for selection bias

The unadjusted and bias-adjusted contingency tables are presented in Table 2. Before adjustment for incomplete ascertainment of cases among pregnancies that were terminated, the odds ratio for prepregnancy obesity (obese vs. not obese) and spina bifida was 1.48 (95% confidence interval: 1.26, 1.73) (Table 3). The adjusted number of cases was calculated by applying w_T to terminated cases in the study and $w_{\bar{T}}$ to live-born and stillborn cases within strata of obese and nonobese women. The odds ratio adjusted for selection bias was 1.26 (95% confidence interval: 1.04, 1.53), given our assumptions.

To allow for uncertainty in the estimates of $P(T|Dx)$ and $P(T|\bar{Dx})$, we performed a probabilistic bias analysis. We

Table 2. Observed and Bias-Adjusted Contingency Tables for Prepregnancy Obesity (Exposure) and Spina Bifida (Outcome), Selected Sites of the National Birth Defects Prevention Study, 1997–2009

Group	Observed		Bias-Adjusted ^a	
	Obese	Not Obese	Obese	Not Obese
Case	239	690	290.2	978.7
Control	1,477	6,297	1,477.0	6,297.0

^a Adjusted for selection bias due to incomplete ascertainment of cases among pregnancies terminated after a prenatal diagnosis of spina bifida.

assigned $P(T|Dx)$ a triangular distribution based on the systematic review of pregnancy termination after prenatal diagnosis with spina bifida (16). We chose a triangular distribution because it allowed specification of a maximum probability corresponding to the point estimate that we hypothesized to be most likely and decreasing probability of selection on either side of that value. The lower and upper limits of the distribution defined the hypothesized minimum and maximum plausible estimates. We fixed the mode of the distribution to equal the overall frequency of termination of pregnancies diagnosed prenatally with spina bifida in the United States (0.49), and we set the lower limit of the distribution to be the lowest proportion reported (0.36) and the upper limit to be the highest proportion reported (0.82) for studies in

the United States. For $P(T|\overline{Dx})$, we used a triangular distribution with a mode of 0.03 (Web Appendix 2), a lower limit of 0.00, and an upper limit of 0.06. We performed 10,000 iterations of the bias analysis. Given our assumptions, the median bias-adjusted odds ratio was 1.22, with a 95% simulation interval including random error of 0.97–1.47 (Table 3).

Confounding example

To illustrate adjustment for selection bias in the presence of confounding, we assumed that race/ethnicity was a confounder (Figure 2A) and recreated Table 1 for each stratum of race/ethnicity (Web Table 1). The first 6 rows were available from NBDPS, and $P(T|Dx)$, $P(T|\overline{Dx})$, and $P(S|\overline{T})$ were unchanged because they were not affected by race/ethnicity. Race/ethnicity-specific weights were calculated based on the new values and applied in models that were adjusted for race/ethnicity. The results were similar to those from models in which no confounding was assumed (Table 3).

For simplicity, we assumed that prepregnancy obesity was only associated with pregnancy termination through prenatal diagnosis. However, this may be incorrect. For example, a sociocultural factor could affect both prepregnancy obesity and termination of pregnancy through a path that does not include prenatal diagnosis (Figure 3). In fact, the prevalence of prepregnancy obesity varies by race/ethnicity (31), as does the probability of terminating a pregnancy after a prenatal diagnosis (9, 32, 33). Thus, race/ethnicity might represent the

Table 3. Unadjusted and Selection Bias-Adjusted Associations Between Prepregnancy Obesity (Obese vs. Not Obese) and Spina Bifida, Selected Sites of the National Birth Defects Prevention Study, 1997–2009

Analysis	Model ^a											
	1				2				3			
	OR	95% CI	Median OR ^b	95% SI ^c	OR	95% CI	Median OR ^b	95% SI ^c	OR	95% CI	Median OR ^d	95% SI ^e
Uncorrected	1.48	1.26, 1.73			1.49	1.27, 1.75			1.49	1.27, 1.75		
Simple selection bias correction ^e	1.26	1.04, 1.53			1.28	1.06, 1.56			1.34	1.11, 1.62		
Probabilistic selection bias correction			1.22	0.97, 1.47			1.22	1.01, 1.46			1.29	1.07, 1.53

Abbreviations: CI, confidence interval; OR, odds ratio; SI, simulation interval.

^a Model 1 was unadjusted for race/ethnicity (Figure 2B). Model 2 was adjusted for race/ethnicity, assuming Figure 2A is correct (race/ethnicity as a confounder). Model 3 was adjusted for race/ethnicity, assuming Figure 3 is correct (race/ethnicity as the sociocultural factor).

^b Probabilistic weight applied to terminated cases using formulas from Table 1 and a triangular distribution (minimum, mode, maximum) of (0.36, 0.49, 0.82) for the proportion of all prenatally diagnosed cases that were terminated and (0.00, 0.03, 0.06) for the proportion of all cases that were not prenatally diagnosed and terminated. A weight of 1.00 was applied to live born and stillborn cases and a weight of 1.00 was applied to controls.

^c The 2.5th to 97.5th percentiles of the corrected OR after incorporating random error sampled from a normal distribution with a mean of 0 and a standard deviation equal to the standard error for the uncorrected OR (for model 1, the standard deviation was 0.0804; for models 2 and 3, it was 0.0808).

^d Probabilistic weight applied to terminated cases using formulas from Table 1 and a triangular distribution (minimum, mode, maximum) for the proportion of prenatally diagnosed cases that were terminated of (0.38, 0.51, 0.84) for white cases, (0.22, 0.35, 0.68) for black cases, (0.18, 0.31, 0.64) for Hispanic cases, and (0.37, 0.50, 0.83) for cases of other races and a triangular distribution for the proportion of all cases that were not prenatally diagnosed and terminated of (0.00, 0.01, 0.04) for white cases, (0.03, 0.06, 0.09) for black cases, (0.00, 0.02, 0.05) for Hispanic cases, and (0.00, 0.03, 0.06) for cases of other races. A weight of 1.00 was applied to live born and stillborn cases and a weight of 1.00 was applied to controls.

^e A weight of 3.86 was applied to terminated cases, a weight of 1.00 was applied to liveborn and stillborn cases, and a weight of 1.00 was applied to controls.

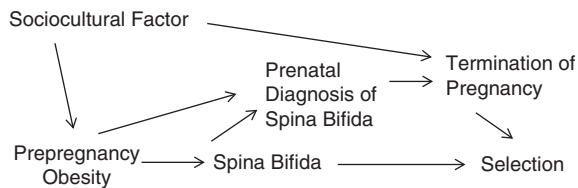


Figure 3. This directed acyclic graph expands Figure 2B to include an unmeasured sociocultural factor (e.g., race/ethnicity) that affects prepregnancy obesity and the likelihood of termination of pregnancy.

sociocultural factor (instead of being a confounder). If Figure 3 is correct, race/ethnicity-specific weights must be calculated using data from NBDPS and race/ethnicity-specific values of $P(T|Dx)$ and $P(T|\overline{Dx})$ abstracted from the literature (Web Table 2). The results adjusted for selection bias based on Figure 3 are closer to the unadjusted odds ratio than are results from previous scenarios, although they are still closer to the null than to the unadjusted results (Table 3).

DISCUSSION

In the present paper, we illustrated a simple method to account for selection bias due to incomplete ascertainment of birth defect cases among pregnancies that are terminated, and we further adapted this method into a probabilistic bias analysis to incorporate uncertainty about the estimates used to calculate the IPSWs. In addition, we illustrated the application of this method in the presence of confounding and in a more complex scenario in which the exposure is associated with termination of pregnancy through a path that does not involve prenatal diagnosis.

All bias-adjusted estimates for prepregnancy obesity and spina bifida were closer to the null than to the unadjusted odds ratio, which is consistent with our initial hypothesis about the likely direction of bias (up and away from the null). We suspected that obese women with pregnancies affected by spina bifida were overrepresented in the study compared with women who were not obese because fetuses of obese women were less likely to be diagnosed prenatally, and therefore the pregnancy was less likely to be terminated. In our analyses, however, our calculated probability of prenatal diagnosis was greater in obese women than in women who were not obese (e.g., 0.70 vs. 0.66 in Table 1). This result highlights the value of quantitatively evaluating bias in epidemiologic studies because our intuitions might lead us astray (19).

If, as our estimates suggest, fetuses of obese women are more likely to be prenatally diagnosed with spina bifida than are fetuses of women who are not obese, then our DAG (Figure 2B) might be correct, but our hypothesized mechanism (that spina bifida is more difficult to visualize on the ultrasound in obese women) might be incorrect. Alternatively, spina bifida could be more difficult to visualize by ultrasound in obese women, but obese women could be more likely to receive prenatal testing because of the suspicion that they are at higher risk of having an affected pregnancy. In fact, in a study in which they examined obesity and detection of fetal anomalies, Dashe et al. (14)

reported that the likelihood of anomalies being detected decreased as BMI increased for routine ultrasounds, but this difference was attenuated for ultrasounds performed for high-risk pregnancies. The relatively small difference between the probabilities could also be due to chance, in which case there should not be an arrow between prepregnancy obesity and prenatal diagnosis in the DAG. There may be other possible mechanisms that would be consistent with the estimated probabilities of prenatal diagnosis among obese and nonobese women.

As with any bias analysis, the validity of our results is conditional on our assumptions being correct. Although we cannot verify our assumptions, they were informed by the current evidence available in the literature and can easily be varied to assess the range of possible bias given different plausible scenarios. However, our example did not take into account other sources of bias, such as misclassification, other types of selection bias, and bias due to missing data. These other sources of bias could be addressed through multiple-bias analysis (19).

Although our method focused on selection bias among the cases, a similar approach could be used to evaluate bias that might arise from incomplete selection of controls among terminated pregnancies. However, in many studies, such as NBDPS, controls are only selected from live births, so $P(S|T) = 0$, and therefore the IPSW would be undefined. Nevertheless, if the distribution of prepregnancy obesity in control women is representative of the distribution of prepregnancy obesity in the source population, any bias would likely be minimal.

Although adjustment for bias is often done to obtain a more valid estimate of a causal effect, the association we investigated does not have a straightforward causal interpretation because of practical limitations of birth defect studies. A detailed discussion of methodologic issues in conducting etiologic studies of birth defects is beyond the scope of this paper, but we will briefly highlight some issues of concern. The research question we would like to answer is whether or not prepregnancy obesity causes spina bifida. Ideally, this question would be addressed among all conceptions, including those that ended in spontaneous abortions. However, including spontaneous abortions is rarely possible because they are often unrecognized, and even among recognized losses, it is difficult to identify birth defects. Bias can occur when spontaneous abortions are excluded but both the exposure and the outcome affect the probability of pregnancy loss (1). Even a causal interpretation of the association between prepregnancy obesity and spina bifida conditional on surviving to 13 weeks' gestation may be questionable if prepregnancy obesity affects pregnancies that terminate before 13 weeks (34). Further, any causal interpretation of our results is limited by the fact that being obese might not be exchangeable with not being obese (35). Thus, even bias-adjusted results should be interpreted with caution.

Exclusion or incomplete ascertainment of birth defects cases among terminated pregnancies poses a continuing challenge to research on birth defects (36). Studies have found substantial differences in the estimated prevalence of many types of birth defects depending on whether cases among terminated pregnancies were included and depending on the source used to ascertain these cases (e.g., hospitals vs. prenatal clinics) (13, 17, 18). Even with multiple sources of ascertainment, birth

defect surveillance programs typically cannot achieve complete case ascertainment among terminated pregnancies, and the proportion of missed cases remains unknown but is likely substantial for some defects, such as spina bifida.

Our approach allows the potential impact of this mechanism of selection bias to be assessed without requiring knowledge of the proportion of cases missed. In fact, it estimates this probability, $P(S|T)$, under specific assumptions. In this example, the probability of selection among all terminated affected pregnancies was 21%, indicating that NBDPS sites that ascertained cases among terminated pregnancies might be missing 79% of terminated, affected pregnancies. Although our assumptions are unverifiable, this estimate indicates the potential for substantial underascertainment given a plausible scenario. In addition to estimating bias-adjusted odds ratios, our method could be adapted to estimate the completeness of case ascertainment by surveillance systems (which might require estimating some values not collected by the surveillance system, e.g., $P(Dx|T, Ob, S)$).

The proposed method for calculating IPSWs allows us to quantitatively estimate the magnitude of bias introduced by incomplete ascertainment of cases among terminated pregnancies, given several assumptions. The method is simple to implement, and the information needed to calculate the IPSWs is available from the literature and directly from the study in some cases. Further, the method can be adapted to address more complex scenarios, such as situations in which confounding is present or the hypothesized DAG is different. Although the proposed bias adjustment does not guarantee an unbiased association, it provides the opportunity to quantitatively explore alternative explanations for the observed unadjusted results and to improve our understanding of the uncertainty in these results due to selection bias. This attention to an important potential source of systematic error can only improve our ability to draw conclusions about a study compared with strictly qualitative attempts to consider the likely role of selection bias.

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(Appendix follows)

APPENDIX 1

Below, we provide a detailed derivation of equation 1, which is used to estimate $P(Dx|Ob)$. The estimate of $P(Dx|Ob)$ is derived from the following equation:

$$P(Dx|\bar{T}, Ob, S) = \frac{P(\bar{T}, Ob, S|Dx)P(Dx)}{P(\bar{T}, Ob, S|Dx)P(Dx) + P(\bar{T}, Ob, S|\bar{Dx})P(\bar{Dx})}.$$

We know that

$$\begin{aligned} P(\bar{T}, Ob, S|Dx) &= P(Ob|Dx)P(\bar{T} |Ob, Dx)P(S|\bar{T}, Ob, Dx) \\ &= P(Ob|Dx)[1 - P(T|Ob, Dx)]P(S|\bar{T}, Ob, Dx). \end{aligned}$$

We assumed that

$$P(T|Ob, Dx) = P(T|Dx)$$

and

$$P(S|\bar{T}, Ob, Dx) = P(S|\bar{T}).$$

After substitution, we get

$$P(\bar{T}, Ob, S|Dx) = P(Ob|Dx)[1 - P(T|Dx)]P(S|\bar{T}).$$

We know that

$$P(Ob|Dx) = P(Dx|Ob)P(Ob)/P(Dx).$$

After substitution, we get

$$P(\bar{T}, Ob, S|Dx) = P(Dx|Ob)P(Ob)[1 - P(T|Dx)]P(S|\bar{T})/P(Dx).$$

Similarly, it can be shown that

$$P(\bar{T}, Ob, S|\bar{Dx}) = P(\bar{Dx}|Ob)P(Ob)[1 - P(T|\bar{Dx})]P(S|\bar{T})/P(\bar{Dx}).$$

We can now substitute into the original equation for $P(Dx|\bar{T}, Ob, S)$ to get the following:

$$P(Dx|\bar{T}, Ob, S) = \frac{\left[\frac{P(Dx|Ob)P(Ob)[1 - P(T|Dx)]P(S|\bar{T})}{P(Dx)} \right] P(Dx)}{\left[\frac{P(Dx|Ob)P(Ob)[1 - P(T|Dx)]P(S|\bar{T})}{P(Dx)} \right] P(Dx) + \left[\frac{P(\bar{Dx}|Ob)P(Ob)[1 - P(T|\bar{Dx})]P(S|\bar{T})}{P(\bar{Dx})} \right] P(\bar{Dx})},$$

which simplifies to

$$P(Dx|\bar{T}, Ob, S) = \frac{P(Dx|Ob)[1 - P(T|Dx)]}{P(Dx|Ob)[1 - P(T|Dx)] + P(\bar{Dx}|Ob)[1 - P(T|\bar{Dx})]}.$$

We know that

$$P(\bar{Dx}|Ob) = 1 - P(Dx|Ob).$$

After substitution, we get

$$P(Dx|\bar{T}, Ob, S) = \frac{P(Dx|Ob)[1 - P(T|Dx)]}{P(Dx|Ob)[1 - P(T|Dx)] + [1 - P(Dx|Ob)][1 - P(T|\bar{Dx})]}.$$

Now, we want to solve for $P(Dx|Ob)$, as follows:

$$\begin{aligned}
 P(Dx|Ob) &= \frac{P(Dx|\bar{T}, Ob, S)}{[1 - P(T|Dx)]} \{P(Dx|Ob)[1 - P(T|Dx)] + [1 - P(Dx|Ob)][1 - P(T|\bar{Dx})]\} \\
 P(Dx|Ob) &= P(Dx|\bar{T}, Ob, S)P(Dx|Ob) + \frac{P(Dx|\bar{T}, Ob, S)}{[1 - P(T|Dx)]} [1 - P(Dx|Ob)][1 - P(T|\bar{Dx})] \\
 P(Dx|Ob)[1 - P(Dx|\bar{T}, Ob, S)] &= \frac{P(Dx|\bar{T}, Ob, S)}{[1 - P(T|Dx)]} [1 - P(Dx|Ob)][1 - P(T|\bar{Dx})] \\
 \frac{P(Dx|Ob)}{[1 - P(Dx|Ob)]} &= \frac{P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]}{[1 - P(T|Dx)][1 - P(Dx|\bar{T}, Ob, S)]} \\
 \frac{[1 - P(Dx|Ob)]}{P(Dx|Ob)} &= \frac{[1 - P(T|Dx)][1 - P(Dx|\bar{T}, Ob, S)]}{P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]} \\
 \frac{1}{P(Dx|Ob)} - 1 &= \frac{[1 - P(T|Dx)][1 - P(Dx|\bar{T}, Ob, S)]}{P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]} \\
 \frac{1}{P(Dx|Ob)} &= \frac{[1 - P(T|Dx)][1 - P(Dx|\bar{T}, Ob, S)]}{P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]} + 1 \\
 \frac{1}{P(Dx|Ob)} &= \frac{[1 - P(T|Dx)][1 - P(Dx|\bar{T}, Ob, S)] + P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]}{P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]}
 \end{aligned}$$

Equation 1:

$$P(Dx|Ob) = \frac{P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]}{[1 - P(T|Dx)][1 - P(Dx|\bar{T}, Ob, S)] + P(Dx|\bar{T}, Ob, S)[1 - P(T|\bar{Dx})]}$$

The derivation of equation 2 for $P(Dx|\bar{Ob})$ parallels the derivation of equation 1 for $P(Dx|Ob)$.

APPENDIX 2

Below, we provide a detailed derivation of equation 3, which is used to estimate $P(S|T)$.

For both women who were obese and those who were not, we directly observed the number of cases that were prenatally diagnosed and in which the pregnancy was terminated (M_1 and M_2) among women with estimated dates of delivery by December 31, 2005 (the last time women were asked about prenatal diagnosis). These counts are equal to the following:

$$M_1 = N_1 P(Dx|Ob) P(T|Dx) P(S|T)$$

and

$$M_2 = N_2 P(Dx|\bar{Ob}) P(T|Dx) P(S|T),$$

where N_1 is the number of obese women who carried fetuses with spina bifida that reached a gestational age of at least 13 weeks (approximately the earliest gestational age at which spina bifida could be prenatally diagnosed) (21) and N_2 is the corresponding number of nonobese women. N_1 , N_2 , and the probabilities in the equations above refer to pregnancies with estimated due dates in the same timeframe as the pregnancies contributing to M_1 and M_2 .

We can rearrange the equations and add them together to get the following:

$$N_1 + N_2 = \frac{M_1}{P(Dx|Ob)P(T|Dx)P(S|T)} + \frac{M_2}{P(Dx|\bar{Ob})P(T|Dx)P(S|T)}.$$

Similarly, we directly observe the number of liveborn and stillborn cases in the study born to obese and nonobese women (Q_1 and Q_2) with estimated dates of delivery by December 31, 2005. Q_1 is equal to the following:

$$Q_1 = N_1 [P(\bar{Dx}|Ob)P(\bar{T}|\bar{Dx})P(S|\bar{T}) + P(Dx|Ob)P(\bar{T}|Dx)P(S|\bar{T})],$$

where N_1 and the probabilities in the equation refer to the same timeframe as Q_1 . We know that

$$P(\overline{Dx}|Ob) = 1 - P(Dx|Ob),$$

$$P(\overline{T}|\overline{Dx}) = 1 - P(T|\overline{Dx}),$$

and

$$P(\overline{T}|Dx) = 1 - P(T|Dx).$$

After substitution, we get

$$Q_1 = N_1 \{ [1 - P(Dx|Ob)][1 - P(T|\overline{Dx})]P(S|\overline{T}) + P(Dx|Ob)[1 - P(T|Dx)]P(S|\overline{T}) \}.$$

By rearranging, we get

$$Q_1 = N_1 P(S|\overline{T}) \{ [1 - P(Dx|Ob)][1 - P(T|\overline{Dx})] + P(Dx|Ob)[1 - P(T|Dx)] \}$$

$$Q_1 = N_1 P(S|\overline{T}) [1 - P(Dx|Ob) - P(T|\overline{Dx}) + P(Dx|Ob)P(T|\overline{Dx}) + P(Dx|Ob) - P(Dx|Ob)P(T|Dx)]$$

$$Q_1 = N_1 P(S|\overline{T}) [1 - P(T|\overline{Dx}) + P(Dx|Ob)P(T|\overline{Dx}) - P(Dx|Ob)P(T|Dx)].$$

Similarly, Q_2 can be shown to be equal to the following:

$$Q_2 = N_2 P(S|\overline{T}) [1 - P(T|\overline{Dx}) + P(Dx|\overline{Ob})P(T|\overline{Dx}) - P(Dx|\overline{Ob})P(T|Dx)].$$

We can rearrange the equations and add them together to get the following:

$$N_1 + N_2 = \frac{Q_1}{P(S|\overline{T}) [1 - P(T|\overline{Dx}) + P(Dx|Ob)P(T|\overline{Dx}) - P(Dx|Ob)P(T|Dx)]}$$

$$+ \frac{Q_2}{P(S|\overline{T}) [1 - P(T|\overline{Dx}) + P(Dx|\overline{Ob})P(T|\overline{Dx}) - P(Dx|\overline{Ob})P(T|Dx)]}.$$

Next, we set the 2 expressions for $N_1 + N_2$ equal to each other and solve for $P(S|T)$ as follows:

$$\frac{M_1}{P(Dx|Ob)P(T|Dx)P(S|T)} + \frac{M_2}{P(Dx|\overline{Ob})P(T|Dx)P(S|T)}$$

$$= \frac{Q_1}{P(S|\overline{T}) [1 - P(T|\overline{Dx}) + P(Dx|Ob)P(T|\overline{Dx}) - P(Dx|Ob)P(T|Dx)]}$$

$$+ \frac{Q_2}{P(S|\overline{T}) [1 - P(T|\overline{Dx}) + P(Dx|\overline{Ob})P(T|\overline{Dx}) - P(Dx|\overline{Ob})P(T|Dx)]}.$$

$$\frac{1}{P(S|T)} \left[\frac{M_1}{P(Dx|Ob)P(T|Dx)} + \frac{M_2}{P(Dx|\overline{Ob})P(T|Dx)} \right]$$

$$= \frac{Q_1}{P(S|\overline{T}) [1 - P(T|\overline{Dx}) + P(Dx|Ob)P(T|\overline{Dx}) - P(Dx|Ob)P(T|Dx)]}$$

$$+ \frac{Q_2}{P(S|\overline{T}) [1 - P(T|\overline{Dx}) + P(Dx|\overline{Ob})P(T|\overline{Dx}) - P(Dx|\overline{Ob})P(T|Dx)]}.$$

Thus, equation 3 equals the following:

$$P(S|T) = \frac{\frac{M_1}{P(Dx|Ob)P(T|Dx)} + \frac{M_2}{P(Dx|\overline{Ob})P(T|Dx)}}{\frac{Q_1}{P(S|\overline{T})[1 - P(T|\overline{Dx}) + P(Dx|Ob)P(T|\overline{Dx}) - P(Dx|Ob)P(T|Dx)]} + \frac{Q_2}{P(S|\overline{T})[1 - P(T|\overline{Dx}) + P(Dx|\overline{Ob})P(T|\overline{Dx}) - P(Dx|\overline{Ob})P(T|Dx)]}}$$

We assume the selection probabilities based on women with estimated dates of delivery by December 31, 2005, do not change over time and the weights based on these probabilities can be applied to cases whose mothers with estimated dates of delivery after that date.