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Assessing the impact of exposure misclassification in case-control studies of self-reported medication use

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Abstract

Background: Empirically evaluating the potential impact of recall bias on observed associations of prenatal exposures to medications is crucial.

Objective: We sought to assess the effects of exposure misclassification on previous studies of the use of non-steroidal anti-inflammatory drugs (NSAIDs) in early pregnancy and increased risk of amniotic bands syndrome (ABS).

Methods: Using data from the National Birth Defects Prevention Study (NBDPS) on births from 1997 to 2011, we included 189 mothers of infants with ABS and 11,829 mothers of infants without congenital anomalies. We identified external studies of medication use during pregnancy to obtain validity parameters for a probabilistic bias analysis to adjust for exposure misclassification. Due to uncertainty about the transportability of these parameters, we conducted multidimensional bias analyses to explore combinations of values on the results.

Results: When we assumed higher specificity in cases or higher sensitivity in controls, misclassification-adjusted estimates suggested confounding-adjusted estimates were attenuated. However, in a few cases, when we assumed greater sensitivity in the cases than the controls (and $Sp \geq 0.9$), the misclassification-adjusted estimates suggested upward bias in the confounding-adjusted estimates.

Conclusions: Results from our bias analysis highlighted that the magnitude of bias depended on the mechanism and the extent of misclassification. However, the parameters available from the

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Conflicts of interest

The authors declare no conflicts of interest.

validation studies were not directly applicable to our study. In the absence of reliable validation studies, considering mechanisms of bias and simulation studies to outline combinations of plausible scenarios to better inform conclusions on the effects of these medications on pregnancy outcomes remains important.

Keywords

epidemiological biases; misclassification; anti-inflammatory agents; non-steroidal; congenital abnormalities

Background

In retrospective studies of medication use during pregnancy, exposure status based on the mother's recall may lead to inaccurate measurement, resulting in non-differential or differential misclassification, the latter often referred to as "maternal recall bias."¹⁻³ Analyses to address such biases are limited by available validation studies. Usually, validation studies estimate the sensitivity and specificity of self-report compared to prescription drug databases. However, pregnancy often leads to medication discontinuation, even when prescribed.⁴⁻⁸ People may be incorrectly classified as exposed despite discontinuing their medications, thus lowering specificity. Additionally, many medications taken during pregnancy are over-the-counter (OTC), and these data are not captured in prescription databases.⁴⁻⁸ These limitations render multidimensional bias analyses necessary to assess the susceptibility of results to the choice of parameters on estimates of medication effects on congenital anomalies.

We use previous research on non-steroidal anti-inflammatory drugs (NSAIDs) and amniotic band syndrome (ABS) as a motivating example to ground this methodological exploration. Nearly 23% of pregnant people in the United States report NSAID use during the first trimester, with estimates of OTC use up to 19%.⁹⁻¹² NSAIDs decrease prostaglandin production, potentially modifying implantation of the embryo, placental development, and maintenance of the pregnancy.¹³⁻¹⁶ NSAIDs may also contribute to vascular disruption, a process linked to several congenital anomalies, including amniotic bands syndrome (ABS).¹⁷⁻²⁴ Vascular disruption can occur in early pregnancy following the ingestion of specific exposures.²⁴⁻²⁸ Since episodic NSAID use during pregnancy is so common, even small increases in risks of congenital anomalies can have a significant public health impact.²⁹

Two studies from the National Birth Defects Prevention Study (NBDPS) have reported adjusted odds ratios (OR) of 1.3 (95% confidence interval [CI] 0.8, 1.8) and 1.4 (95% CI 0.9, 2.1) for associations between use of non-aspirin NSAIDs and ABS.^{17,18} Results from a Norwegian cohort study suggest that exposure to NSAIDs was not associated with an increased risk of several congenital anomalies.²⁹ However, due to small numbers of NSAID-exposed infants in individual categories, several congenital anomalies were excluded from the analyses, including ABS.²⁹ This analysis investigates the impact of exposure misclassification on the association between NSAIDs and ABS in NBDPS.^{30,31}

Methods

Case-control selection

NBDPS was a multi-site, population-based case-control study designed to investigate more than 30 major structural anomalies. Cases and controls born between October 1997 and December 2011 were identified using surveillance systems in ten states across the U.S. Eligible cases included live born, stillborn (≥ 20 weeks' gestation), and terminations at selected sites. Congenital anomalies with a known genetic cause were excluded. Controls were randomly selected among live births without a major congenital anomaly from birth certificates or hospital birth records in the same region, with an estimated delivery date during the same period as cases.^{32,33} Overall, 67% of eligible cases and 65% of eligible controls participated in interviews.³²

Mothers of eligible cases and controls were sent introductory packets and invited to complete computer-assisted telephone interviews (CATI) in English or Spanish between 6 weeks to 24 months after the estimated delivery date (EDD). The interviews included detailed questions on demographics, reproductive factors, behaviours, illnesses, medications, and other exposures that occurred three months before conception through the end of the pregnancy.³²

Outcome

Case classification has been described in detail elsewhere.³²⁻³⁴ Briefly, cases in NBDPS were classified as isolated, multiple, or complex by study geneticists. Isolated cases refer to cases with single major defects (including single major defects accompanied by minor defects in the absence of a defined syndrome) and multiple major defects in the same organ system, presumed to reduce pathogenetic heterogeneity.³²⁻³⁴ This study only includes isolated ABS cases.

Isolated ABS cases involved constriction band(s), cord constriction, unusual syndactylies (particularly acrosyndactyly), and amputations only affecting the limbs (i.e., no craniofacial disruption or truncal involvement). ABS cases with reported anomalies consistent with limb-body wall complex were not considered. Among the 284 ABS case mothers, we excluded 95 (33%) mothers of infants with non-isolated cases of ABS. We also excluded one (<1%) participant with missing information on the estimated date of delivery information (EDD). Following exclusions, we retained 189 ABS case mothers and 11,829 control mothers in our analytic sample.

Exposure

The exposure of interest is any reported use of non-aspirin NSAIDs in the periconceptional period – defined as the month preceding conception to the third month of pregnancy, compared to no use of non-aspirin NSAIDs. Mothers with missing information on exposure to NSAIDs were excluded from the analysis ($n = 339$). Information on use of non-aspirin NSAIDs was compiled and coded using the Slone Drug Dictionary.³⁵ Participants were considered exposed if they reported any use of the following medications (both prescription and OTC) during the exposure window: aceclofenac, choline magnesium trisalicylate,

etodolac, ibuprofen, indomethacin, ketoprofen, ketorolac, magnesium salicylate, methyl salicylate, nabumetone, naproxen, phenyl salicylate, sodium salicylate, sulindac, tolmetin and zomepirac. Participants reporting use of aspirin, regardless of NSAID use, were excluded from this analysis.

Covariates

We considered study site, demographic, and clinical characteristics as covariates. Demographic information included age at delivery (< 20, 20–24, 25–29, ≥30 years), education (≤ 12, 13–15, ≥16 years), and race/ethnicity (non-Hispanic Black, non-Hispanic white, Hispanic, Asian, Native American, and other racial category). Mothers reporting Hispanic ethnicity were classified as Hispanic, regardless of reported race. Other variables included pre-pregnancy body mass index (BMI) (<18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m² according to the National Institutes of Health categories), number of previous live births (≥ 1, 0) and pregnancy intention.

We also examined alcohol consumption and cigarette smoking in the preconception period (defined as the three months before conception) as potential confounders of the association between ABS and non-aspirin NSAIDs. Reported alcohol consumption was categorized as binge drinking (≥ 4 drinks/occasion), drinking but not binge drinking (<4 drinks/occasion), and no drinking. Cigarette smoking was dichotomized into <15 and ≥15 cigarettes per day. Women who reported different average daily amounts of smoking between months during the period of interest were assigned the highest value of reported cigarettes.

Conventional analysis

Descriptive analyses included estimating the distribution of maternal factors (i.e., age, BMI, education, race/ethnicity, number of previous births, and pregnancy intention), cigarette smoking, and alcohol consumption. Original analyses of these data presented multivariable-adjusted models using Firth's penalized logistic regression models to estimate adjusted odds ratios (OR) and profile-based likelihood 95% confidence intervals (CI) to mitigate bias due to sparse data.^{17,36} Maternal age at delivery and education were categorized into dichotomous variables (age: <25, ≥25 years; education <12 and ≥12 years). For race/ethnicity, mothers reporting Asian or Native American as their racial identity were reclassified as "Other racial category" due to small cell sizes.

Missing data

To be consistent with the previous complete case analyses of these data, participants with missing data on any of the covariates were not included in the adjusted regression model. Covariates with missing information considered in the final regression models included racial identity, formal education, previous live births, smoking and alcohol consumption. Overall, we excluded 5.3% of cases (n=10) and 3.4% of controls (n = 400) with missing covariate information in the final regression models.

Adjustment for exposure misclassification

We considered sensitivity (Se) and specificity (Sp) from external validation studies of medication use.^{5,6,37} We did not identify existing studies that reported Se and Sp of non-

aspirin NSAIDs by case-control status using a “gold standard.” Available validation studies on self-reported use of NSAIDs during pregnancy (among cases or controls) relied on two types of imperfect “gold standard” approaches. The first approach uses electronic medical records (EMR) and pharmacy records as the “gold standard.” This gold standard does not accurately capture OTC medications. The second approach relied on contemporaneous diary information, first prompting participants to document NSAID use during the first trimester prospectively, then asking participants to recall their previously reported use at the end of the first trimester. While this approach captures the use of OTC medications, we hypothesise that diary recording will likely enhance retrospective recall, and the recall interval is shorter than that in NBDPS. Neither of these sources of ‘gold standard’ exposure information is ideal or directly applicable to NBDPS. Given these limitations, we could not assume that Se and Sp were transportable to the NBDPS population. While the external validation studies suggest that specificity may be nearly perfect and sensitivity is poor, there is a wide range of uncertainty regarding the values assigned to the parameters. Thus, we also conducted multidimensional non-probabilistic quantitative bias analyses to explore combinations of values of the bias parameters.

For cases (D_1), we used data from a validation study from Eurocat Northern Netherlands, a population-based registry of congenital anomalies.⁶ Pharmacy records were used as the “gold standard” and compared to questionnaires to assess SeD_1 (0.36, 95% CI 0.16, 0.56) and SpD_1 (0.98, 95% CI 0.96, 0.99) of maternal recall of medication use in the three months before and during pregnancy (Table 1.3, *van Gelder et al.*)⁶ For controls (D_0), we used results from a validation study on medication exposures during pregnancy of women with chronic conditions but births without a congenital anomaly.⁸ Pregnant participants were recruited in three cohorts at <20 weeks’ gestation and completed three to four telephone interviews. Validity parameters [$SeD_0 = 0.38$ (95% CI 0.23, 0.55), $SpD_0 = 0.93$ (95% CI 0.88, 0.95)] for medication use were calculated using agreement between maternal report and obstetrician records (including active medication lists and physicians’ notes) (Table 4.3, *Palmsten et al.*)⁸.

We obtained a second set of bias parameters for controls, $SeD_0 = 0.79$ (95% CI 0.61, 0.96) and $SpD_0 = 0.62$ (95% CI 0.47, 0.78), from a validation study using a subset of the *Right from the Start* (RFTS) community-based cohort (2006–2012). Daily diaries prompted participants to record NSAID use. In the third trimester, participants were asked to retrospectively report information on medications, mainly targeting NSAIDs during the periconceptional period. Retrospective information was compared to prospectively collected data from daily dairies (Table 4.3, *Sundermann et al.*)⁵

Non-probabilistic bias analysis

For non-probabilistic bias analyses, we calculated misclassification-adjusted ORs that do not consider uncertainty in the bias parameters and, therefore, do not allow us to calculate uncertainty intervals for the estimate.³⁰ To investigate differential recall, we assumed different scenarios anchored on assumptions of better classification in cases and small between-group differences. First, we assumed $SpD_1 > SpD_0$ ($SpD_1 = SpD_0 + 0.05$) and assigned the same value for Se in both groups. Then, we assumed $SeD_0 > SeD_1$ ($SeD_0 =$

SeD₁+0.1) and assigned the same value for Sp in both groups. Results from a recent study of medication use in a population-based case-control study of birth defects suggested that sensitivity is higher in cases compared to controls. However, specificity may be lower for medications with episodic use, differing from the previous validation studies.³⁸ Therefore, we assumed SeD₁ > SeD₀ (SeD₁= SeD₀+0.1) and SpD₁ = SpD₀. We then calculated the minimum bias parameters yielding non-zero cells. Due to exposure distribution, the minimum values for cases were SeD₁=0.28, SpD₁=0.72, and for controls, were SeD₀=0.23, SpD₀=0.77. As the full range of values from the selected external validation studies results in impossible values, we focused on the values from those studies compatible with our data. We computed bias-adjusted ORs for SeD₀ and SeD₁ values over a range from 0.3 to 0.7, while values for SpD₀ and SpD₁ ranged from 0.8 to 1.0. We also examined non-differential exposure misclassification concerning the outcome.

Probabilistic bias analysis

For the probabilistic analyses, we randomly sampled values for Se and Sp from triangular (lower limit *a*, upper limit *b*, mode *c*) distributions with correlated sampling, using the ranges presented in the validation studies as the minimum *a*, maximum *b*. Correlated sampling assumes that extreme differences in classification for the cases and controls are unlikely, even with the assumption of differential misclassification, since the same classification method was used for both groups.³⁹ This avoids unrealistically assuming that the distributions of Se and Sp for cases and controls are independent.³⁹ We assumed a correlation of 0.8 for both Se and Sp.

For SeD₁, we specified a mode of 0.36 (*a* = 0.16, *b* = 0.56) and a mode of 0.98 (*a* = 0.96, *b* = 0.99) for SpD₁ based on parameters from *van Gelder et al.* We specified a mode of 0.38 (*a* = 0.23, *b* = 0.55) for SeD₀ and 0.93 (*a* = 0.88, *b* = 0.85) for SpD₀, based on parameters from *Palmsten et al.* We used these studies' reported 95% CI to generate the upper and lower bounds.

Sensitivity and specificity are related to predictive values via Bayes theorem. Calculating negative and positive predictive values (NPVs and PPVs) also requires the exposure prevalence among D₁ and D₀. To account for this unknown true exposure prevalence, we calculated the expected "truth" based on Se and Sp, using randomly sampled participants classified as exposed and unexposed.³⁹ We used the following equations:

$$\begin{aligned}
 PPV_{D1} &= \frac{Se_{D1}P(E_{D1})}{Se_{D1}P(E_{D1}) + (1 + Sp_{D1})(1 - P(E_{D1}))} \\
 NPV_{D1} &= \frac{Sp_{D1}(1 - P(E_{D1}))}{(1 - Se_{D1})P(E_{D1}) + Sp_{D1}(1 - P(E_{D1}))} \\
 PPV_{D0} &= \frac{Se_{D0}P(E_{D0})}{Se_{D0}P(E_{D0}) + (1 + Sp_{D0})(1 - P(E_{D0}))} \\
 NPV_{D0} &= \frac{Sp_{D0}(1 - P(E_{D0}))}{(1 - Se_{D0})P(E_{D0}) + Sp_{D0}(1 - P(E_{D0}))}
 \end{aligned}$$

We then used Bernoulli trials to simulate new exposure values using the NPVs and PPVs above. We assigned each participant a probability of being truly exposed and truly unexposed, given their observed exposure, outcome status, and NPV and PPV values. A

misclassification-adjusted exposure was then sampled for each person. We imputed each parameter 10,000 times and calculated 10,000 ORs.^{30,31} We then included random error for each bias-adjusted estimate by randomly sampling from a standard normal distribution multiplied by the conventional standard error and subtracting it from the bias-adjusted estimate.³⁹ We present the results as the median of the distribution of bias-adjusted ORs as a point estimate and the 2.5th and 97.5th percentile values as a simulation interval (SI).

Ethics approval

This study was approved by the institutional review boards of the individual NBDPS study centers and the U.S. Centers for Disease Control and Prevention.

Results

Conventional analysis

Among mothers of controls, 22.5% reported use of non-aspirin NSAIDs in the periconceptional period, compared to 26.5% of case mothers (Table 1). There was a higher proportion of ABS mothers who were younger and had lower education attainment than mothers of controls. ABS case mothers were also more likely to report smoking (26.4% vs. 17.5%) and alcohol consumption (43.4% vs. 35.7%) than controls (Table 2). For the association between the use of non-aspirin NSAIDs and ABS, the unadjusted OR was 1.29 (95% CI 0.93, 1.79). After excluding participants with missing covariate information and adjusting for study location, age, education attainment, race, and parity, the adjusted OR was 1.25 (95% CI 0.84, 1.79). After further adjusting for smoking and alcohol consumption, the adjusted OR was 1.17 (95% CI 0.79, 1.69).

Exposure misclassification

The results of the multidimensional bias analyses varied, with some trends emerging. When we assumed $SpD_1 > SpD_0$ and $SeD_1 = SeD_0$, misclassification-adjusted estimates ranged from 1.72 ($SeD_1 = 0.70$, $SpD_1 = 1.0$) to 13.71 ($SeD_1 = 0.30$, $SpD_1 = 0.85$) (Figure 1). When we assumed greater Se in the controls, the resulting misclassification-adjusted estimated ranged from 1.63 ($SeD_0 = 0.8$, $Sp = 1.0$) to 20.82 ($SeD_0 = 0.4$, $Sp = 0.8$) (Figure 2). When we only assumed greater Se for the cases ($SeD_1 > SeD_0$), the misclassification-adjusted estimates ranged from 0.69 to 1.23 ($SpD_1 = 0.9$, 1.0), and 1.45 to 2.29 ($SpD_1 = 0.8$) (Figure 3). When we assumed non-differential misclassification, the bias-adjusted estimates ranged from 1.35 ($Se = 0.7$, $Sp = 1.0$) to 8.49 ($Se = 0.3$, $Sp = 0.8$) (Figure 4). Approximately 18% of iterations produced negative adjusted cell counts in the probabilistic bias analysis. The probabilistic bias-adjusted estimate was 2.45 (95% SI 0.64, 23.99), an imprecise result.

Comment

Principal findings

In a few cases, notably when we assumed $SeD_1 > SeD_0$ (and $Sp \geq 0.9$), the observed estimate was upwardly biased. However, under most scenarios, whether we assumed $SeD_1 > SeD_0$ (and $Sp \leq 0.8$), $SeD_0 > SeD_1$, or $SpD_1 > SpD_0$, misclassification-adjusted estimates suggested that the confounding-only adjusted estimate was downwardly biased. As Sp

and Se decreased in both groups, the misclassification-bias adjusted estimate increased, indicating a higher effect estimate than the previously observed value. Under certain combinations of bias parameters, we observe no bias in (e.g., $SeD_1 (0.8) > SeD_0 (0.7)$; $Sp = 0.9$).

Strengths of the study

A strength of our study is that we examine exposure misclassification and consider both differential and non-differential misclassification, exploring the impact of minor deviations in sensitivity and specificity. A systematic review of the application of bias analyses in the literature noted that studies exploring both mechanisms of misclassification were rare.⁴⁰ We also applied correlated sampling in our probabilistic analyses to decrease the likelihood that highly discrepant parameter values would be selected.⁴¹

Limitations of the data

Our analyses were limited by several factors. In the probabilistic analyses, approximately 18% of our iterations resulted in negative cell counts. This occurs when adjusting for misclassification and values of the proposed parameters are incompatible with the data.³⁹ The majority of the available validation studies on NSAID use during pregnancy compare medical or pharmacy records data to maternal reports. Comparing prescription records to self-report data often shows substantial disagreement between the two information sources.^{6,42} Medications acquired OTC are not captured in prescription records. Therefore, studies using administrative records would consider people unexposed when exposed. Additionally, pregnancy is a major predictor for medication discontinuation. Thus, pregnant people may also be classified incorrectly as exposed when they have, in fact, discontinued or reduced medication use.⁴³

Information on medication use in NBDPS captures information on both prescription and OTC medication use. Using bias parameters informed by pharmacy records limits our ability to effectively ascertain the potential effects of recall bias for a medication that is largely used intermittently.⁴⁴ Additionally, we lacked information on dose and indication in the NBDPS data. Thus we were unable to conduct stratified analyses to explore the degree of misclassification by indication. Bias analyses can still provide valuable contributions including observing changes in results under various realistic assumptions about mechanisms of bias. Multidimensional bias analyses allowed us to assess how robust the observed measure of association is to changes in the bias parameter values, although they generally remain agnostic about which sensitivities and specificities have greater prior probability.^{30,39} Probabilistic bias analyses allow researchers to specify which values for bias parameters are more or less likely based on the assigned probability distributions.^{30,39}

Interpretation

Studies on the accuracy of recall of medication use during pregnancy suggest that sensitivity may be low, particularly with medications taken intermittently, such as analgesics.^{6,42} In rare exposures, the strength of the bias from exposure misclassification is driven by the specificity. When the specificity is relatively high, we would not expect a strong bias despite low sensitivity.^{30,38} In the case of common exposures, we expect losses in sensitivity to

have a substantial impact on misclassification, which we demonstrate in the results of our analyses.^{30,38} Several other factors affect recall of exposures beyond frequency and type of medication, such as age, education, or other pre-pregnancy behaviors associated with social desirability.⁴⁵ Higher levels of education are consistent with better recall, and educational attainment was higher in the controls than in the cases in our data.⁴⁶ In our analyses, we made the assumption that bias parameters only varied by case-control status. While estimating bias parameters conditional on other variables may provide better adjustment for bias, further parsing out our small sample size might have introduced additional bias to the analysis or resulted in non-estimable ORs.⁴⁷

Conclusions

Under the assumption of recall bias, the direction and magnitude of the bias depend on the specific sensitivity and specificity among cases and controls. Our results suggested that decreases in sensitivity may be drastically biasing results downwards and that we may be failing to detect meaningful risks.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Social media quote:

Low sensitivity of reported over-the-counter medication use may be an important threat to validity, despite high specificity. Using an example from the literature, we demonstrate that previous estimates of the association between non-aspirin non-steroidal anti-inflammatory drugs in the periconceptional period and amniotic band syndrome may be attenuated.

Synopsis:**Study question:**

This study examines the impact of exposure misclassification in case-control studies assessing the association between medication use and fetal outcomes, using non-aspirin NSAIDs and amniotic band syndrome (ABS) as an example.

What is already known:

Previous research suggested increased odds of ABS with periconceptional NSAID use. However, reliance on retrospective self-reports can introduce misclassification in case-control studies.

What this study adds:

In several instances, bias analyses adjusting for exposure misclassification suggested that previously reported associations of NSAIDs and ABS were attenuated, albeit estimates were imprecise. In rare exposures, the specificity drives the strength of the bias from exposure misclassification. However, results from our analyses suggested that despite high specificity, in some cases, losses in sensitivity can result in strong bias in effect estimates.

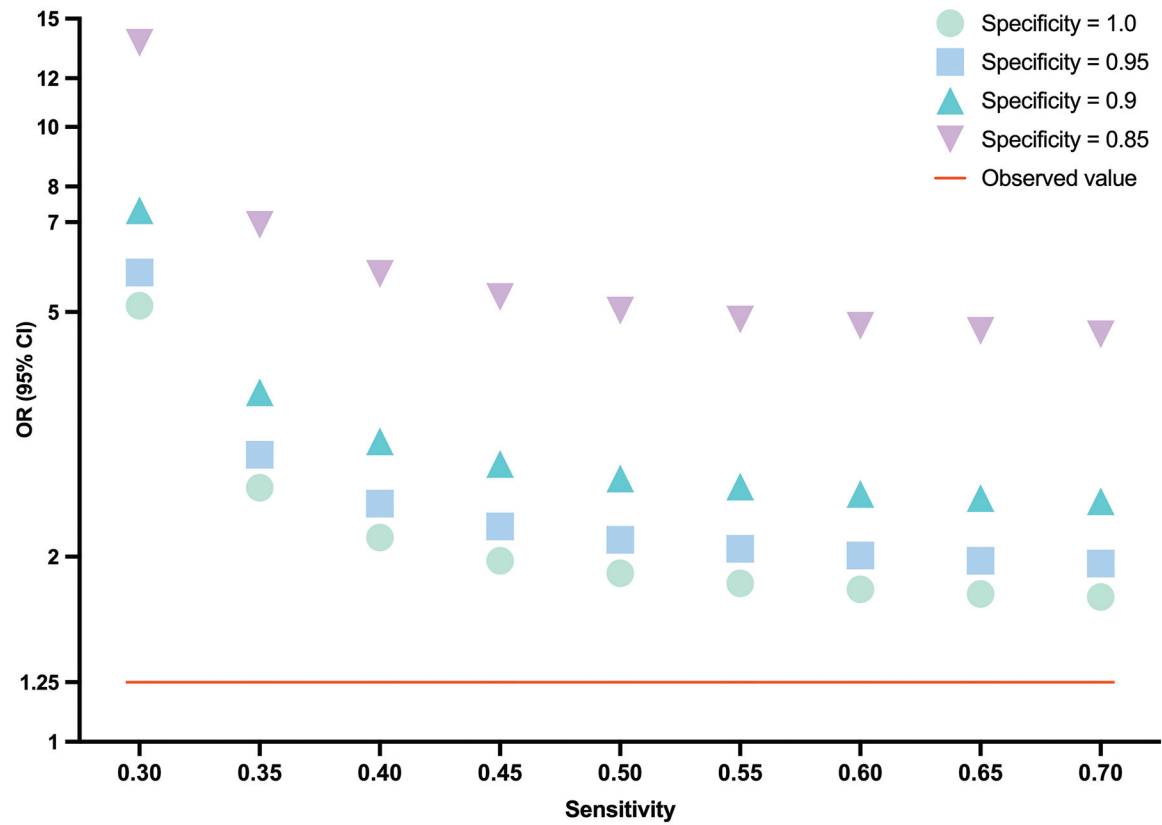


Figure 1. Misclassification-adjusted estimate(s) for differential exposure misclassification, assigning identical values for SeD_1 and SeD_0 ($Se = 0.3-0.7$) and $SpD_1 = SpD_0 + 0.05$ ($SpD_0 = 0.8-0.95$)

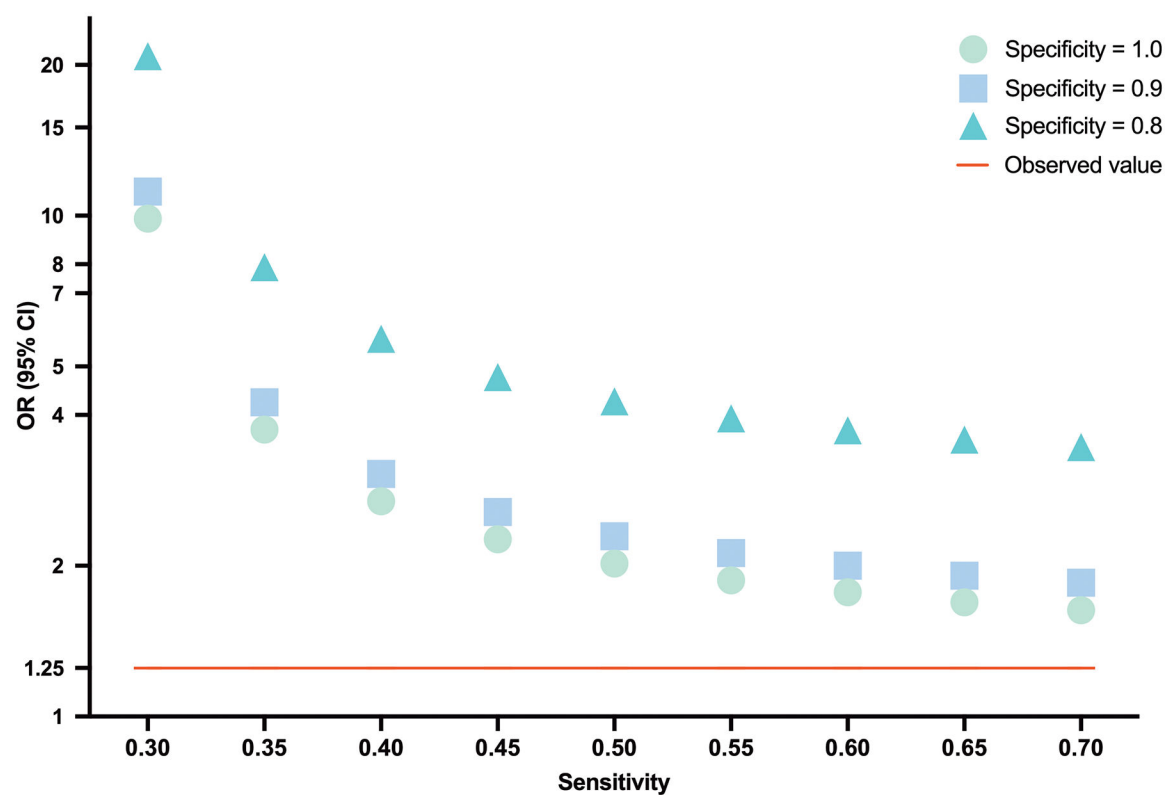


Figure 2.
Misclassification-adjusted estimate(s) for differential exposure misclassification, assigning $SeD_0 = SeD_1 + 0.10$ ($SeD_0 = 0.4-0.8$) and $SpD_0 = SpD_1$ ($Sp = 0.8-1.0$)

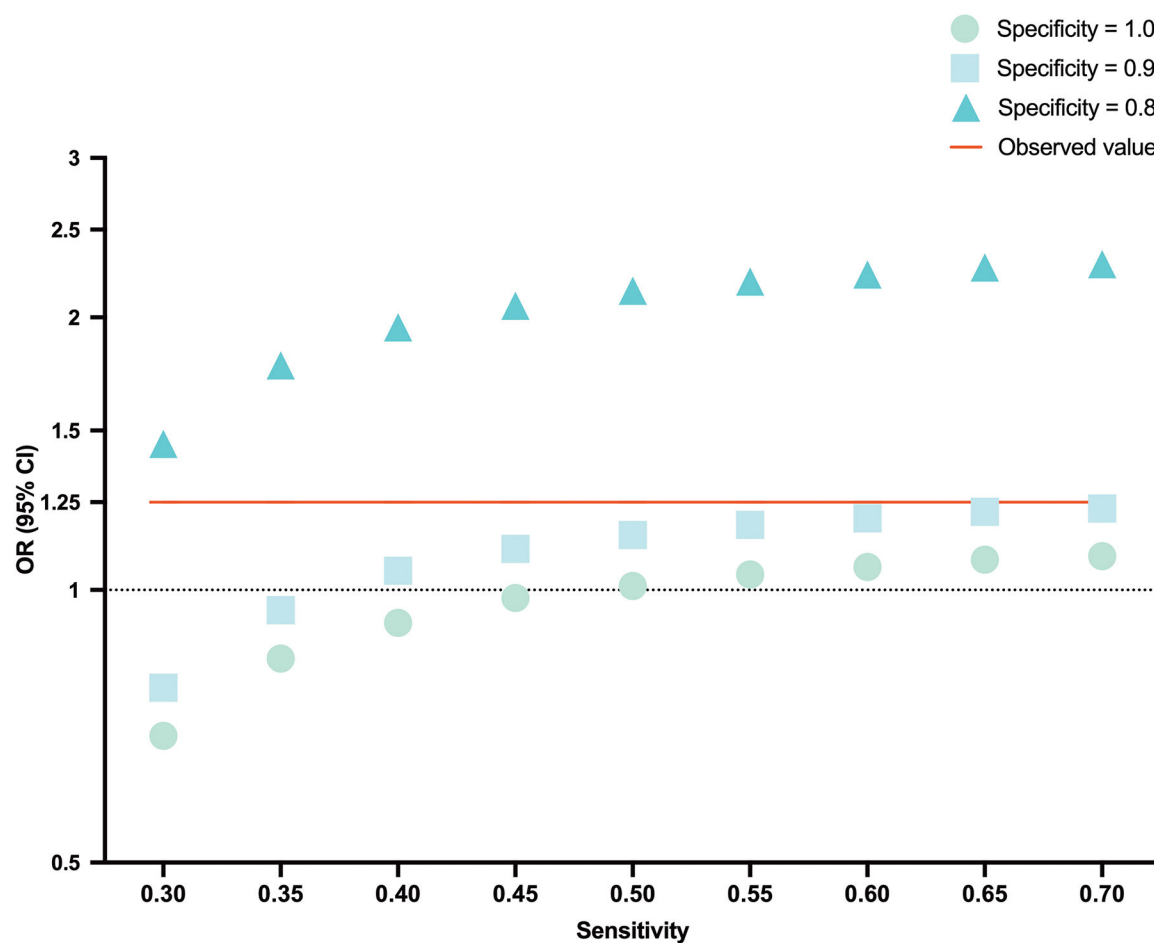


Figure 3. Misclassification-adjusted estimate(s) for differential exposure misclassification, $SeD_1 = SeD_0 + 0.10$ ($SeD_1 = 0.4-0.8$), and $SpD_0 = SpD_1$ ($Sp = 0.8-1.0$)

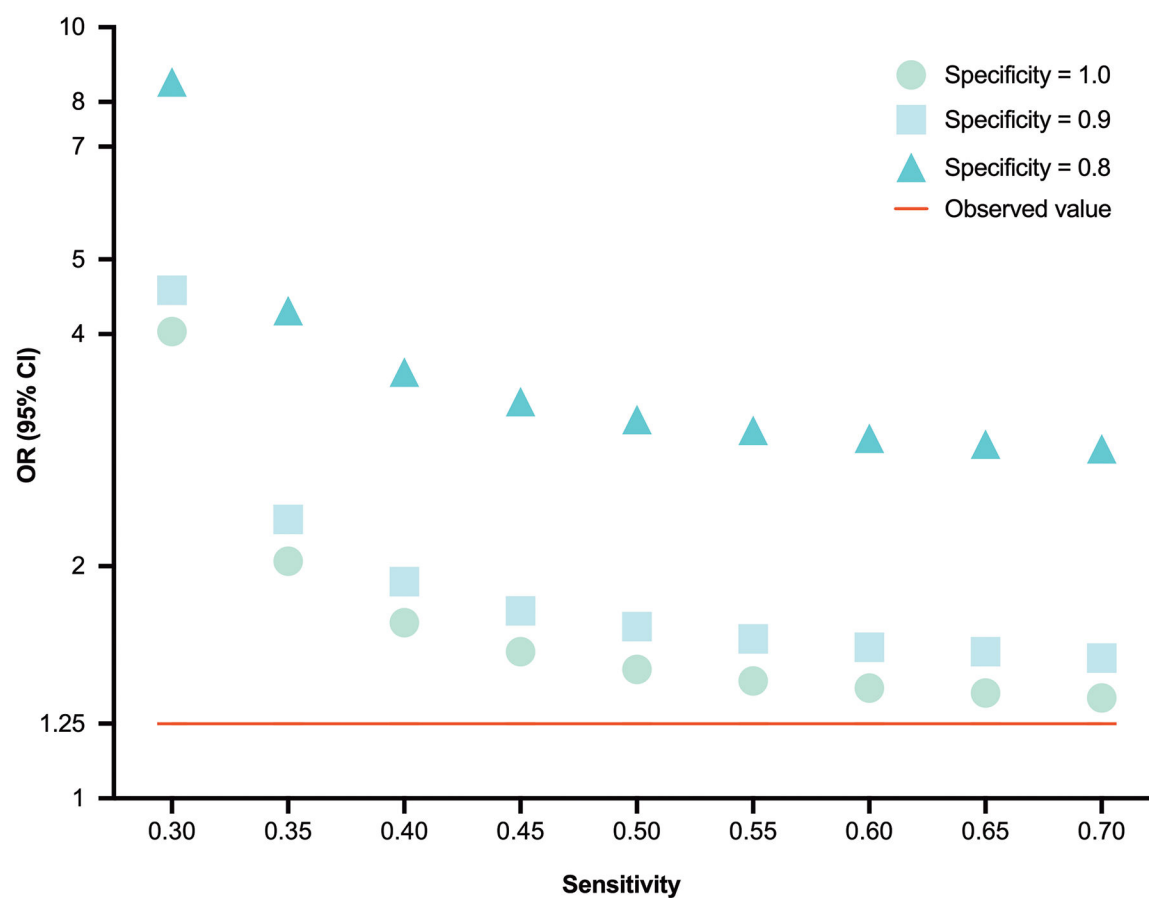


Figure 4. Misclassification-adjusted estimate(s) for nondifferential exposure misclassification, $SeD_0 = SeD_1$ ($Se = 0.3-0.7$) and $SpD_0 = SpD_1$ ($Sp = 0.8-1.0$)

Table 1.

Characteristics of Mothers of ABS^a Cases and Controls in the Analysis, National Birth Defects Prevention Study, 1997–2011.

	Isolated ABS (n = 189)		Controls (n = 11,829)	
	No.	%	No.	%
Non-aspirin NSAID				
Yes	50	26.5	2,658	22.5
No	129	68.3	8,842	74.7
Missing/Unknown	10	5.3	329	2.8
Maternal age, years				
< 20	34	18.0	1,177	10.0
20-24	65	34.4	2,668	22.6
25-29	41	21.7	3,271	27.7
30+	49	25.9	4,713	39.8
Maternal BMI, kg/m ²				
Underweight (<18.5)	10	5.3	599	5.1
Normal weight (18.5 – <25)	103	54.5	6,045	51.1
Overweight (25 – <30)	30	15.9	2,557	21.6
Obese (30+)	34	18.0	2,074	17.5
Out of range/Missing	12	6.4	554	4.7
Maternal education, years				
≤ 12	97	51.3	4,630	39.1
13–15	45	23.8	3,079	26.0
≥ 16	40	21.2	3,775	31.9
Missing	7	3.7	345	2.9
Maternal race/ethnicity				
Black	44	23.3	1,308	11.1
White	93	49.2	6,836	57.8
Hispanic	36	19.1	2,908	24.6
Asian	7	3.7	353	3.0
Native American	1	0.5	51	0.4
Other racial categories/Missing	8	4.2	373	3.2
Number of previous live births				
None	110	58.2	4,664	39.4
1+	75	39.7	7,114	60.1
Missing	4	2.1	51	0.4
Pregnancy intention				
Wanted ^b	135	71.4	8,486	71.7
Unwanted	21	11.1	1,115	9.4
Missing/Refused/Unknown	33	17.5	2,228	18.8

^aAmniotic band syndrome

^bIncludes "mistimed" and "did not care" responses
Percents may not add to 100% due to rounding

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Table 2.

Periconceptional Health Behaviors among Mothers of ABS^a Cases and Non-malformed Controls, National Birth Defects Prevention Study, 1997–2011.

Exposures	Isolated ABS (n = 189)		Controls (n = 11,829)	
	No.	%	No.	%
Maternal smoking				
≥ 15 cigarettes/day	15	7.9	580	4.9
< 15 cigarettes/day	35	18.5	1,495	12.6
No smoking	132	69.8	9,454	79.9
Missing/Unknown	7	3.7	300	2.5
Alcohol drinking				
Binge drinking (≥ 4 drinks)	34	18.0	1,431	12.1
Drinking but not binge drinking	48	25.4	2,788	23.6
No drinking	98	51.9	7,210	61.0
Missing/Unknown	9	4.8	400	3.4

^aAmniotic band syndrome

Table 3. Validation studies of reported sensitivity and specificity values for reported maternal recall for exposure to analgesics during pregnancy among mothers of infants with and without birth defects.

Validity Measures						
Cases				Controls		
Authors	Sensitivity (95% CI)	Specificity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	"Gold standard" measurement tool (s)
<i>van Gelder MMHI et al.</i>						
	0.36 (0.16, 0.56)	0.98 (0.96, 0.99)	--	--	--	Pharmacy records
<i>Palinsten et al.</i>						
			0.38 (0.23, 0.55)	0.93 (0.88, 0.95)	oral NSAIDs	United States and Canada Medical records
<i>Sundermann et al</i>						
	--	--	0.79	0.62	NSAIDs	United States Prospective diary entries

CI: Confidence Interval; Eurocat –>NNL: European Registration of Congenital Anomalies and Twins Northern Netherlands (EUROCAT>NNL).