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Using Bayesian Models to Assess the Effects of Under-reporting of Cannabis Use on the Association with Birth Defects, National Birth Defects Prevention Study, 1997–2005

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Abstract

Background—Studies on associations between periconceptional cannabis exposure and birth defects have mainly relied on self-reported exposure. Therefore, the results may be biased due to underreporting of the exposure. The aim of this study was to quantify the potential effects of this form of exposure misclassification.

Methods—Using multivariable logistic regression, we re-analyzed associations between periconceptional cannabis use and 20 specific birth defects using data from the National Birth Defects Prevention Study from 1997–2005 for 13 859 case infants and 6556 control infants. For seven birth defects, we implemented four Bayesian models based on various assumptions concerning the sensitivity of self-reported cannabis use to estimate odds ratios (ORs), adjusted for confounding and underreporting of the exposure. We used information on sensitivity of self-reported cannabis use from the literature for prior assumptions.

Results—The results unadjusted for underreporting of the exposure showed an association between cannabis use and anencephaly (posterior OR 1.9 [95% credible interval (CRI) 1.1, 3.2]) which persisted after adjustment for potential exposure misclassification. Initially, no statistically significant associations were observed between cannabis use and the other birth defect categories studied. Although adjustment for underreporting did not notably change these effect estimates, cannabis use was associated with esophageal atresia (posterior OR 1.7 [95% CRI 1.0, 2.9]), diaphragmatic hernia (posterior OR 1.8 [95% CRI 1.1, 3.0]) and gastroschisis (posterior OR 1.7 [95% CRI 1.2, 2.3]) after correction for exposure misclassification.

Conclusions—Underreporting of the exposure may have obscured some cannabis-birth defect associations in previous studies. However, the resulting bias is likely to be limited.

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Valid measurement of exposures, outcomes, and potential confounders is essential in epidemiologic research to prevent information bias.[1] In case-control studies, non-differential or differential misclassification may be present when exposure information is collected after the outcome has occurred. Under certain conditions, non-differential misclassification of a dichotomous variable biases results towards the null value.[2,3] Differential misclassification, on the other hand, may lead to either underestimation or overestimation of the true effect.[1] Multiple methods to correct for potential biases due to misclassification in observational studies have recently been published.[4–7] Although misclassification frequently occurs in epidemiologic research, methods to quantify the resulting bias are rarely used or reported for a variety of reasons, including complexity of reporting and a lack of demand.[4,8] However, this does not justify lack of attention to potential bias in observed exposure-outcome associations that may result from ignoring misclassification.[9,10] In this paper, we present a case study in which adjustments for underreporting of the exposure of interest were made by means of Bayesian methods.

Although maternal cannabis use generally does not appear to be associated with the occurrence of major birth defects,[11–13] increased risks of gastroschisis,[14] isolated simple ventricular septal defects (VSDs),[15] and anencephaly[13] have been reported after prenatal cannabis exposure. As most of these studies used a case-control design and all used self-reported modes of data collection for exposure assessment (either maternal interviews or medical chart reviews), non-differential or differential misclassification of cannabis use may have occurred and subsequently may have biased the results. It is very likely that the use of cannabis was underestimated in these studies, because some subjects would have falsely denied use for fear of judgment or prosecution.[16] Although misclassification of cannabis use during pregnancy was generally acknowledged, no attempts were made to quantify the effect of underreporting on cannabis-birth defect associations. In this study, we used data from the National Birth Defects Prevention Study (NBDPS) to estimate odds ratios and interval estimates adjusted for underreporting of the exposure for the associations between periconceptional cannabis use and selected birth defects.

METHODS

Data

The NBDPS is a multi-site population-based case-control study of more than 30 types of major birth defects that started enrollment of women with an estimated date of delivery on or after October 1, 1997.[17] Case infants (live born, stillborn, or induced abortions) were identified using existing birth defects surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Information on birth defects abstracted from hospital records was reviewed by a clinical geneticist at each study center to determine eligibility. The methods used for case classification in the NBDPS have been described in detail elsewhere.[18] Control infants were randomly selected from all live-born infants without any major birth defect from the same geographical area and time period using either hospital birth records (Arkansas, California, Georgia 1997–2000, New York, and Texas) or birth certificates (Georgia 2001–2005, Iowa, Massachusetts, New Jersey, North Carolina, and Utah). Computer-assisted telephone interviews were

conducted with the mothers of case and control infants between 6 weeks and 24 months after the estimated date of delivery, including questions on demographic factors, medical and pregnancy history, lifestyle, and occupation. For the time period of interest, the interview participation rate was 69% for case mothers and 66% for control mothers.

In this study, exposure to cannabis was defined as any reported use of marijuana or hashish in the period from 1 month before pregnancy to the end of the third month of pregnancy (periconceptional period). Only case and control infants whose mothers did not report use of any illicit drugs in the 3 months before pregnancy and during the entire index pregnancy, were considered unexposed.

The current study included case and control infants born from October 1, 1997 through December 31, 2005, whose mothers completed the interview (n = 18 745 and 6703, respectively). This dataset overlaps to a large extent with the dataset used by van Gelder *et al.* to study associations between periconceptional illicit drug use and birth defects,[13] but it contains 2 additional years of data. Only case infants diagnosed with one of the 20 birth defect categories selected by van Gelder *et al.*[13] (n = 14 429) were included in this study. Analogous to our previous study, infants born to women who reported preexisting diabetes type 1 or type 2 (298 cases and 39 controls) were excluded because of the strong association with major birth defects,[19] as well as infants only exposed to other types of illicit drugs (84 cases and 30 controls) or with missing information on illicit drug exposure (188 cases and 78 controls) because of our exposure definition. Eventually, we analyzed data on 13 859 case infants and 6556 control infants.

Statistical analysis

We first repeated our earlier analyses[13] using the updated dataset. In these analyses, multivariable logistic regression techniques were used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for periconceptional cannabis use and each of the 20 selected birth defects. The same confounder set used in the previous study, consisting of maternal age at delivery, race/ethnicity, level of education, smoking in the periconceptional period, binge drinking in the periconceptional period (≥4 drinks per episode), prepregnancy body mass index, and any use of folic acid or multivitamins containing folic acid in the month before pregnancy or in the first month of pregnancy, was included in all current multivariable analyses. The re-analysis was performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL).

As data on the validity of the interview data on periconceptional cannabis use were not available, we used information on sensitivity of self-reports from the literature. We are not aware of any studies that provide information on accuracy of cannabis reporting among mothers of infants with birth defects. However, we identified 5 studies which determined the sensitivity of interview data on cannabis use among pregnant and postpartum women (Table 1).[20–24] These studies reported sensitivities ranging from 0.58 to 0.82. Because falsely reporting cannabis use is very unlikely, we assumed specificity to be 1.00 in all analyses. These parameters were used in Bayesian models to adjust the cannabis-birth defect associations for non-differential or differential underreporting. These analyses were performed using WinBUGS version 1.4 from within R version 2.12.2 for Windows[25] for 7

birth defect groups: all defects that had an elevated OR for periconceptional cannabis use in the frequentist re-analysis (i.e. anencephaly, esophageal atresia, diaphragmatic hernia, and gastroschisis), 1 defect with a decreased OR for periconceptional cannabis use (hypospadias), 1 defect that has been associated with periconceptional cannabis use in previous studies but not in our re-analysis (perimembranous VSD), and 1 defect with a relatively large case group that was not associated with periconceptional cannabis use (cleft lip ± cleft palate).

Following the framework of MacLehose *et al.*,[6] we conducted Bayesian uncertainty analyses conditional on prior hypotheses generated from published studies. In short, 3 models, an outcome model, an exposure model, and a measurement model, were jointly estimated, which allowed simultaneous imputation of the true periconceptional cannabis exposure status and estimation of its effect on the risk of the selected birth defects. In the outcome model, the odds of an infant having the selected birth defect was modeled with a logistic regression model conditional on the (unknown) periconceptional cannabis exposure status and the potential confounders assuming no interaction between cannabis use and other factors:

$$logit\left(Pr\left(BD_i=1\right)\right)=\beta_0+\beta_1 can_i^{true}+z_i^{'}\theta$$

where BD_i is case/control status, β_1 is the effect of periconceptional cannabis use, can_i^{true} is the unobserved true periconceptional cannabis exposure status, and θ is a vector of effects of the potential confounders in the vector z_i'. We used a non-informative normal distribution with mean = 0 and variance = 10^6 for the prior distribution of the intercept. Informative priors were placed on the remaining parameters (Table 2). These prior distributions were informed using prior studies, which were discussed among a panel of experienced researchers in the field of birth defects epidemiology, consisting of 2 of the authors and 3 experts outside the study team. As an example, we assumed folic acid supplementation to have no additional protective effect on folate-sensitive birth defects (normal distribution, mean = 0, variance = 0.13), because all pregnant women in our study were exposed to folic acid through food fortification.[26] Priors on coefficients for which no information from previous studies was available and the prior on the effect of periconceptional cannabis use on the risk of birth defects were kept relatively vague (normal distribution, mean = 0, variance = 0.67; corresponding to a prior OR of 1.0 with a 95% credible interval of [0.2, 5.0]) as we were uncertain about the magnitude of the ORs for these associations.

In the exposure model, we modeled the probability of true exposure to cannabis in the periconceptional period conditional on a set of predictors:

$$logit\left(Pr\left(can_i^{true}=1\right)\right)=\omega_0+z_i^{'}\omega$$

where ω is a vector of the effects of the predictors in z_i'. The set of predictors consisted of all potential confounders and paternal cannabis use, which is highly predictive of maternal

illicit drug use.[27,28] However, as is discussed by MacLehose *et al.*,[6] it is difficult to inform priors for parameter estimates because the outcome of interest, true exposure to cannabis, is generally not observed in studies. Therefore, we also placed vague priors (normal distribution, mean = 0, variance = 0.67) on the coefficients in this model.

Finally, in the measurement model we modeled the probability of reporting periconceptional cannabis use during the interview dependent on the true (but unobserved) exposure status and the case/control status, which allowed us to introduce differential misclassification. Because we assumed specificity to be 1.00, we could simplify the measurement model used by MacLehose *et al.*[6] to:

$$P\left(can_i^{int}=1\right)=a_0 \times can_i^{true} \times (1-BD_i)+a_1 \times can_i^{true} \times BD_i$$

Here can_i^{int} is the periconceptional cannabis exposure status the woman reported in the interview, α_0 is the sensitivity of reported cannabis use among control mothers, , and α_1 is the sensitivity of reported cannabis use among case mothers. The exposure and measurement models were used to impute values of can_i^{true} in a way similar to that used with Bayesian missing data techniques.[6] These imputed values were then used to estimate the associations between periconceptional cannabis use and the selected birth defects.

To quantify the potential effects of underreporting of the exposure on the cannabis-birth defect associations observed, we implemented four scenarios that specified a_0 and a_1 in the measurement model. In Scenario 1, the reference scenario, we assumed sensitivity to equal 1.00 (no correction for underreporting), which resulted in a standard Bayesian logistic regression model. Scenario 2 is based on the assumption that cannabis exposure status was non-differentially misclassified with a sensitivity fixed at 3 different values: 0.80, 0.65, and 0.50. In case-control studies of birth defects, there is evidence that maternal reporting is not affected by pregnancy outcome.[29,30] However, since recall bias cannot be excluded, it was assumed that the cannabis exposure status was differentially misclassified for Scenario 3, with the assumed sensitivity to be 0.05 or 0.10 lower among controls than the fixed values of 0.80 and 0.65 among cases. Scenario 4 was based on the assumption that the sensitivities used in the measurement model are not exactly known. For the prior distribution of the sensitivity, a beta distribution ($\alpha = 15$, $\beta = 6.5$) was chosen with prior parameters selected to reflect a priori beliefs concerning reported cannabis use, i.e. sensitivity with a mean of 0.7 and a standard deviation of 0.1. The values for sensitivity among cases and controls were assumed not to be correlated.

We conducted a sensitivity analysis to determine the influence of our prior assumptions in the exposure and outcome models by placing vague priors on all coefficients in every model. All models were fitted using Markov chain Monte Carlo algorithms, which were run for 20 000 iterations with the first 1000 iterations excluded as a burn-in period. We ran three chains from different initial positions; convergence was monitored with trace plots and the Gelman-Rubin statistic. After the burn-in period, the iterations of the algorithm were random draws from the posterior distributions of interest, of which the median was exponentiated to obtain

the OR of interest. We exponentiated the 2.5th and 97.5th percentile of the random draws to obtain 95% posterior credible intervals (CRIs). To provide a measure of precision of the CRIs, we calculated the half width ratio by dividing the half-width of the CRI by the median. The R script and model specifications used are shown in Appendix S2.

RESULTS

A total of 825 mothers (4.0%) reported use of cannabis in the periconceptional period: 4.1% of the case mothers and 3.8% of the control mothers. The ORs for periconceptional cannabis use adjusted for confounding observed in the original and updated datasets for each of the birth defects studied are shown in Table 3. In general, the results from the replication analyses were comparable with the ORs reported earlier.[13] In the updated dataset, periconceptional cannabis use was more strongly associated with anencephaly (aOR = 2.2 [95% CI 1.3, 3.7]) and indications were found for associations with esophageal atresia (aOR = 1.4 [95% CI 0.8, 2.4]), diaphragmatic hernia (aOR = 1.4 [95% CI 0.9, 2.2]), and gastroschisis (aOR = 1.2 [95% CI 0.9, 1.7]). No associations were observed between cannabis use in the periconceptional period and any of the other 16 birth defect categories.

In the Bayesian assessment, the observed ORs for the associations between the potential confounders and the selected birth defects (Appendix S3) were for the most part consistent with the prior specifications (Table 2). All models converged relatively quickly. The posterior ORs and 95% CRIs for the associations between periconceptional cannabis use and the 4 selected birth defects with elevated ORs in the replication analyses are shown in Table 4. After adjustment for non-differential underreporting (Scenario 2), we observed associations between cannabis use in the periconceptional period and anencephaly with posterior ORs of 2.0 [95% CRI 1.2, 3.4], 2.1 [95% CRI 1.2, 3.4], and 2.0 [95% CRI 1.2, 3.3] for assumed sensitivities of 0.80, 0.65, and 0.50, respectively (Figure 1a). In addition, periconceptional cannabis use seemed to be associated with esophageal atresia, diaphragmatic hernia, and gastroschisis with posterior ORs of 1.6 [95% CRI 0.9, 2.5], 1.8 [95% CRI 1.2, 2.7], and 1.6 [95% CRI 1.2, 2.2], respectively (Scenario 2, sensitivity 0.50). As expected, the elevated posterior ORs were slightly diminished compared to Scenario 2 after adjusting for the possibility of recall bias (Scenario 3), but still resulted in increased ORs for anencephaly, diaphragmatic hernia, and gastroschisis. Estimates from Scenario 4, which treated the sensitivity as unknown, showed increased posterior ORs after periconceptional cannabis use for anencephaly (OR = 2.1 [95% CRI 1.2, 3.6]), esophageal atresia (OR = 1.7 [95% CRI 1.0, 2.9]), diaphragmatic hernia (OR = 1.8 [95% CRI 1.1, 3.0]), and gastroschisis (OR = 1.7 [95% CRI 1.2, 2.3]) with wider CRIs compared with Scenario 1.

For hypospadias, perimembranous VSD, and cleft lip ± cleft palate, no statistically significant posterior ORs were observed after adjustment for underreporting in all Scenarios studied (Table 5). However, the risk of hypospadias seemed to be decreased after adjustment for differential misclassification with the lowest value being 0.7 (95% CRI 0.5, 1.0; sensitivity among cases 0.80, sensitivity among controls 0.70). Again, the CRIs were wider in Scenario 4 than in the other Scenarios.

The results of the sensitivity analyses indicated that placing vague priors on the coefficients in the outcome and exposure models did not change the results substantially (Appendix S4). However, the posterior ORs for the association between periconceptional cannabis use and anencephaly were slightly higher with wider posterior CRIs in the sensitivity analysis compared with the main analysis.

COMMENTS

The results from our frequentist replication analysis were very similar to the results reported previously.[13] We applied Bayesian methods to estimate the potential effects of exposure misclassification on cannabis-birth defects associations because the joint estimation of the outcome, exposure, and measurement model is relatively straightforward in Bayesian inference, especially when compared with frequentist inference.[6] After adjustments for underreporting of the exposure, the OR estimates for the associations between periconceptional cannabis use and the 7 selected birth defects did not change considerably compared with the naïve Scenario assuming no misclassification and were very consistent across all Scenarios, even with sensitivities as low as 0.50. However, we found statistically significant associations between periconceptional cannabis use and the occurrence of anencephaly and gastroschisis in all Scenarios studied. In addition, increased odds ratios for esophageal atresia and diaphragmatic hernia were observed among infants exposed to cannabis in the periconceptional period in Scenarios 2 and 4 and in some cases of Scenario 3.

Although the differences with the naïve Scenario were small, the OR estimates obtained in Scenario 2, which corrected for non-differential misclassification with sensitivity as a known constant, were in the expected direction for most defects.[2,3] For hypospadias, however, the corrected ORs seem to move towards the null, indicating that the commonly-used assumption that non-differential misclassification results in smaller effect estimates is not sufficient.

In case of recall bias, one would expect associations to be biased away from the null (i.e. an overestimation of the effect). However, since the sensitivity among cases was also not assumed to be perfect in Scenario 3, the ORs observed in this Scenario do not necessarily have to be lower than those observed in Scenario 1. When comparing Scenarios 2 and 3 for the fixed sensitivity values of 0.80 and 0.65 (similar to the sensitivity among cases in Scenario 3), we indeed observed slightly lower ORs after adjustment for differential misclassification.

Ideally, data obtained from a validation study conducted within the NBDPS should be used to quantify sensitivity and specificity of self-reported cannabis exposure status as these measures may vary across settings. However, due to the retrospective study design, we could only use external validation data, which were collected years before the start of the NBDPS in different populations (Table 1). Because participants in the validation studies were told about the testing procedures which may have increased reporting of exposure, we used somewhat lower values for sensitivity in our analyses than those observed in these studies. As a consequence, Scenario 4, which treated sensitivity as unknown, is of particular

interest in this case, although the choice for a prior distribution for this parameter may be debated. We applied the same beta distribution to both the sensitivity among cases and controls, which were assumed to be independent. In future work, models allowing correlation between the sensitivities, as proposed by Greenland and Gustafson,[31] could be applied. In Scenario 4, the posterior ORs observed were larger than those produced in the other Scenarios, which is comparable with the pattern observed by MacLehose *et al*.[6]

Although the OR estimates adjusted for underreporting of cannabis use in the periconceptional period followed expectation with regard to the direction of the resulting bias, the results only slightly changed after correction for misclassification. This may have been due to the relatively low exposure prevalence in the study population. Larger changes in effect estimates for the association between periconceptional maternal smoking, which is much more common than cannabis use, and orofacial clefts were observed in a study using the same Bayesian methods,[6] adding credibility to this explanation. However, despite the limited size of the changes, some associations that were not statistically significant in the naïve models reached statistical significance after correction for underreporting, suggesting that some associations may be overlooked if exposure misclassification is not taken into account.

When accounting for any source of bias, adjustments lead to a widening of intervals. In the Scenarios with fixed sensitivity values, we did not observe this widening of CRIs as we did not incorporate additional uncertainty into the models. However, in Scenario 4, in which additional uncertainty with respect to sensitivity values was incorporated, we did see the expected widening of the CRIs.

In addition to the use of external validation data, our approach has other limitations as well. We assumed that the specificity of the interview was 1.00 and that no measurement error was present in the confounding and outcome variables, so we cannot rule out that other types of error biased our results. The models used in this framework could be adapted to incorporate imperfect specificity of the measurement instrument and other sources of bias if reasonable prior values are available.[6] Furthermore, we excluded infants born to women with preexisting diabetes as these were omitted from our previous study,[13] which we wanted to mirror as closely as possible. Extensions to the work presented here could consist of including this group of subjects, as well as additional analyses on cases with isolated defects only and subjects without a positive family history of the birth defect under study.

Exposure misclassification may have a serious impact on the validity of epidemiologic studies. The best solution is to measure exposures without error, but this is often impossible. Sensitivity analyses, such as the Bayesian approach presented in this paper, may provide insight into the possible impact of exposure misclassification on the effect estimates. In the case of cannabis-birth defect associations, underreporting of the exposure may have obscured other possible associations, including those between periconceptional cannabis use and the occurrence of esophageal atresia, diaphragmatic hernia, and gastroschisis. Furthermore, the analyses indicated that it is unlikely that the association between exposure to cannabis in the periconceptional period and anencephaly observed in the standard logistic regression analysis can be explained by exposure misclassification. However, the OR

estimates only slightly changed after correction for misclassification. As stated previously,[6] it is doubtful that further case-control studies will be able to answer the question whether these associations are true or not without improvements in the methods of data collection, such as completing interviews as shortly after delivery as possible[32] and the use of a Certificate of Confidentiality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Studies that reported sensitivity values for interview data on cannabis use during pregnancy

Authors	Source population	Years of data collection	Reference	Sensitivity (No. true positives/ Total no. positives)
Frank *et al.*[21]	Boston, USA	1984–1986	Urine samples	0.76 (94/123)
Hingson *et al.*[20]	Boston, USA	1984	Urine samples	0.82 (23/28)
Jacobson *et al.*[23]	Detroit, USA	NR	Antenatal interview	0.75 (44/59)
Ostrea *et al.*[24]	Detroit, USA	NR	Maternal hair + meconium	0.58
Zuckerman *et al.*[22]	Boston, USA	1984–1987	Urine samples	0.74 (149/202)

NR: not reported.

Table 2

Prior odds ratios (95% credible intervals) used in the outcome models[a]

	Anencephaly	Perimembranous VSD	Cleft lip ± cleft palate[1,2]	Esophageal atresia[3,4]	Hypospadias[5,6]	Diaphragmatic hernia[3,7]	Gastroschisis[8]
Reported cannabis use in periconceptional period							
No	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Yes	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]
Maternal age at delivery[9,10]							
<25 years	1.5 [1.0, 2.3]	1.0 [0.5, 2.0]	1.2 [0.8, 1.8]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	3.5 [1.4, 9.0]
25–34 years	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
≥35 years	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.6 [1.0, 2.6]	1.5 [1.0, 2.3]	1.3 [0.7, 2.4]	0.4 [0.2, 0.8]
Race or ethnicity[11-13]							
NH white	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
NH black	0.9 [0.6, 1.4]	0.9 [0.4, 2.0]	0.8 [0.4, 1.6]	0.8 [0.4, 1.6]	0.7 [0.5, 1.0]	0.9 [0.5, 1.6]	0.6 [0.3, 1.2]
Hispanic	1.4 [1.0, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	0.9 [0.5, 1.6]	0.6 [0.4, 1.0]	0.9 [0.5, 1.6]	1.0 [0.5, 2.0]
Other	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]	1.0 [0.2, 5.0]	0.9 [0.5, 1.6]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]
Level of education							
≤12 years	1.3 [0.9, 1.9]	1.0 [0.2, 5.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.3 [0.7, 2.4]
>12 years	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Cigarette smoking in periconceptional period[15]							
No	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Yes	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.4 [1.0, 2.0]	1.0 [0.5, 2.0]	1.2 [0.7, 2.1]	1.0 [0.5, 2.0]	1.6 [1.0, 2.6]
Binge drinking in periconceptional period[15]							
No	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Yes	1.0 [0.2, 5.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.2, 5.0]	1.0 [0.5, 2.0]	1.0 [0.2, 5.0]
Prepregnancy BMI[16,17]							
<30	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
≥30	1.4 [1.0, 2.0]	1.1 [0.6, 2.0]	1.2 [0.8, 1.8]	1.2 [0.9, 1.6]	1.1 [0.7, 1.7]	1.3 [0.9, 1.9]	0.2 [0.1, 0.4]
Periconceptional folic acid use[18]							
No	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Yes	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]	1.0 [0.5, 2.0]

VSD, ventricular septal defect.

[a]The key studies (see Appendix S1 for complete reference) that were used to help inform prior knowledge are indicated in superscript.

Table 3

Observed adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) for the associations between periconceptional cannabis use and selected birth defects. Data from the National Birth Defects Prevention Study (NBDPS), 1997–2005

	NBDPS 1997–2003[a]			NBDPS 1997–2005		
Birth defect	**No. of exposed cases / Total no. of cases**	**aOR [95% CI][b]**		**No. of exposed cases / Total no. of cases**	**aOR [95% CI][b]**	
None [controls]	189/4866	1.0	[Reference]	251/6556	1.0	[Reference]
Anencephaly/craniorachischisis	12/244	1.7	[0.9, 3.4]	18/329	2.2	[1.3, 3.7]
Spina bifida	20/525	1.0	[0.6, 1.6]	24/703	0.9	[0.6, 1.4]
Anotia, microtia	11/287	1.0	[0.5, 2.0]	13/394	0.9	[0.5, 1.7]
D-transposition great vessels	9/336	0.7	[0.3, 1.4]	14/451	0.8	[0.5, 1.5]
Tetralogy of Fallot	19/486	1.1	[0.6, 1.8]	24/657	1.1	[0.7, 1.7]
Hypoplastic left heart	7/247	0.7	[0.3, 1.6]	10/355	0.8	[0.4, 1.5]
Coarctation of the aorta	15/433	1.0	[0.6, 1.8]	21/618	1.2	[0.7, 1.9]
Pulmonary valve stenosis	24/582	1.2	[0.8, 1.9]	32/850	1.0	[0.7, 1.5]
Perimembranous VSD	34/927	0.9	[0.6, 1.4]	52/1363	1.0	[0.8, 1.4]
ASD secundum	31/943	0.7	[0.5, 1.0]	54/1465	0.8	[0.6, 1.1]
ASD not otherwise specified	14/288	1.2	[0.7, 2.2]	22/500	1.1	[0.7, 1.8]
Cleft lip ± cleft palate	61/1269	1.0	[0.7, 1.4]	82/1735	1.0	[0.8, 1.3]
Cleft palate	25/677	0.8	[0.5, 1.3]	38/907	1.0	[0.7, 1.5]
Esophageal atresia	12/329	1.2	[0.6, 2.2]	17/419	1.4	[0.8, 2.4]
Anorectal atresia	13/468	0.7	[0.4, 1.2]	19/605	0.8	[0.5, 1.3]
Hypospadias[c]	20/924	0.7	[0.4, 1.2]	32/1291	0.8	[0.5, 1.2]
Transverse limb deficiency	14/315	1.1	[0.6, 2.0]	16/404	1.0	[0.6, 1.7]
Craniosynostosis	16/517	1.0	[0.5, 1.7]	21/786	0.8	[0.5, 1.3]
Diaphragmatic hernia	19/365	1.3	[0.8, 2.2]	25/498	1.4	[0.9, 2.2]
Gastroschisis	62/485	1.3	[0.9, 1.8]	82/688	1.2	[0.9, 1.7]

ASD, atrial septal defect; VSD, ventricular septal defect.

[a] As reported by van Gelder *et al.*[13]

[b] Adjusted for maternal factors: age at delivery, race or ethnicity, level of education, cigarette smoking, binge drinking, prepregnancy BMI, and periconceptional folic acid use.

[c] Only male control infants included (1997-2003: n = 2452, 4.1% exposed; 1997-2005: n = 3316, 4.1% exposed).

Table 4

Posterior odds ratios (ORs) with 95% credible intervals (CRIs) for the association between periconceptional cannabis use and anencephaly, esophageal atresia, diaphragmatic hernia, and gastroschisis, adjusted for underreporting of the exposure using Bayesian methods. Data from the National Birth Defects Prevention Study, 1997–2005

	Anencephaly			Esophageal atresia			Diaphragmatic hernia			Gastroschisis		
Scenario	**OR**	**[95% CRI]**	**Half width ratio[a]**	**OR**	**[95% CRI]**	**Half width ratio[a]**	**OR**	**[95% CRI]**	**Half width ratio[a]**	**OR**	**[95% CRI]**	**Half width ratio[a]**
No correction for underreporting	1.9	[1.1, 3.2]	0.54	1.3	[0.7, 2.1]	0.53	1.3	[0.9, 2.1]	0.45	1.4	[1.0, 1.9]	0.30
Non-differential underreporting												
Sensitivity 0.80	2.0	[1.2, 3.4]	0.55	1.5	[0.9, 2.4]	0.53	1.5	[0.9, 2.3]	0.46	1.5	[1.1, 2.1]	0.32
Sensitivity 0.65	2.1	[1.2, 3.4]	0.54	1.6	[0.9, 2.5]	0.51	1.7	[1.1, 2.6]	0.45	1.6	[1.2, 2.2]	0.31
Sensitivity 0.50	2.0	[1.2, 3.3]	0.52	1.6	[0.9, 2.5]	0.50	1.8	[1.2, 2.7]	0.43	1.6	[1.2, 2.2]	0.30
Differential underreporting												
Se_{cases} 0.80; $Se_{controls}$ 0.75	1.9	[1.1, 3.2]	0.54	1.4	[0.8, 2.3]	0.53	1.5	[0.9, 2.2]	0.45	1.4	[1.1, 2.0]	0.32
Se_{cases} 0.80; $Se_{controls}$ 0.70	1.8	[1.1, 3.1]	0.54	1.3	[0.8, 2.2]	0.53	1.4	[0.9, 2.1]	0.46	1.4	[1.0, 1.9]	0.32
Se_{cases} 0.65; $Se_{controls}$ 0.60	2.0	[1.1, 3.2]	0.53	1.5	[0.9, 2.4]	0.50	1.6	[1.0, 2.4]	0.44	1.5	[1.1, 2.1]	0.31
Se_{cases} 0.65; $Se_{controls}$ 0.55	1.9	[1.1, 3.0]	0.52	1.4	[0.9, 2.3]	0.50	1.6	[1.0, 2.4]	0.45	1.5	[1.1, 2.0]	0.31
Sensitivity not exactly known	2.1	[1.2, 3.6]	0.59	1.7	[1.0, 2.9]	0.57	1.8	[1.1, 3.0]	0.52	1.7	[1.2, 2.3]	0.35

Se, sensitivity

[a] Half width ratio = ((upper limit 95% CRI - lower limit 95% CRI) / 2) / OR

Table 5

Posterior odds ratios (ORs) with 95% credible intervals (CRIs) for the association between periconceptional cannabis use and hypospadias, perimembranous ventricular septal defects, and cleft lip ± cleft palate, adjusted for underreporting of the exposure using Bayesian methods. Data from the National Birth Defects Prevention Study, 1997–2005

	Hypospadias			Perimembranous VSD			Cleft lip ± cleft palate		
Scenario	**OR**	**[95% CRI]**	**Half width ratio[a]**	**OR**	**[95% CRI]**	**Half width ratio[a]**	**OR**	**[95% CRI]**	**Half width ratio[a]**
No correction for underreporting	0.7	[0.5, 1.1]	0.41	1.0	[0.7, 1.3]	0.32	1.0	[0.8, 1.4]	0.28
Non-differential underreporting									
Sensitivity 0.80	0.8	[0.5, 1.1]	0.41	1.0	[0.7, 1.3]	0.33	1.1	[0.8, 1.4]	0.28
Sensitivity 0.65	0.8	[0.5, 1.2]	0.40	1.0	[0.7, 1.3]	0.32	1.1	[0.9, 1.5]	0.28
Sensitivity 0.50	0.8	[0.6, 1.2]	0.38	1.0	[0.8, 1.4]	0.32	1.2	[0.9, 1.6]	0.27
Differential underreporting									
Se_{cases} 0.80; $Se_{controls}$ 0.75	0.7	[0.5, 1.1]	0.41	0.9	[0.7, 1.3]	0.33	1.0	[0.8, 1.3]	0.28
Se_{cases} 0.80; $Se_{controls}$ 0.70	0.7	[0.5, 1.0]	0.41	0.9	[0.6, 1.2]	0.33	1.0	[0.7, 1.3]	0.28
Se_{cases} 0.65; $Se_{controls}$ 0.60	0.8	[0.5, 1.1]	0.39	0.9	[0.7, 1.3]	0.33	1.1	[0.8, 1.4]	0.27
Se_{cases} 0.65; $Se_{controls}$ 0.55	0.7	[0.5, 1.1]	0.40	0.9	[0.7, 1.2]	0.32	1.0	[0.8, 1.4]	0.28
Sensitivity not exactly known	0.9	[0.6, 1.4]	0.46	1.0	[0.7, 1.4]	0.39	1.2	[0.9, 1.7]	0.34

Se, sensitivity; VSD, ventricular septal defect.

[a] Half width ratio = ((upper limit 95% CRI - lower limit 95% CRI) / 2) / OR