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Periconceptional nonsteroidal anti-inflammatory drug use, folic acid intake, and the risk of spina bifida

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Abstract

Background: Use of nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy may increase risk for neural tube defects (NTDs), including spina bifida. Folic acid intake can prevent NTDs, but it is not known whether it modifies any risks associated with NSAID use.

Objectives: To assess the impact of periconceptional NSAID use on the risk of spina bifida overall and stratified by folic acid intake.

Study Design: We analyzed 1998–2015 data from the Slone Epidemiology Center Birth Defects Study, a multi-site, case–control study. Mothers were interviewed to identify sociodemographic factors, behaviors, and exposures during pregnancy. Periconceptional NSAID use was defined as use of aspirin, ibuprofen, naproxen, or COX2 inhibitors within the month before or after the last menstrual period. Logistic regression models were used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for NSAID use, adjusted for study center and race/ethnicity stratified by average daily folic acid intake above ("high FA") or below ("low FA") 400 mcg/day.

Results: We compared mothers of 267 infants with spina bifida to mothers of 6,233 nonmalformed controls. Among control mothers, 20% used NSAIDS periconceptionally (16% ibuprofen, 4% aspirin, 3% naproxen, and <1% COX-2 inhibitors). For any NSAID use, the aORs among low FA and high FA women were 1.70 (95% CI [1.13, 2.57]) and 1.09 (95% CI [0.69, 1.71]), respectively.

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CONFLICT OF INTERESTS

Daina Esposito is an employee of Moderna and a former employee of HealthCore and Ciconia Inc., which conduct industry-sponsored research unrelated to this work. Allen A. Mitchell is a member of the Tecfidera Pregnancy Exposure Advisory Committee sponsored by Biogen. Other authors have no conflict of interests to declare.

Conclusions: We observed a small increase in the risk for spina bifida among infants born to women who used NSAIDs periconceptionally, but this risk was limited to those who had inadequate folic acid intake.

Keywords

folic acid; neural tube defects; nonsteroidal anti-inflammatory drugs; pregnancy; spina bifida

1 | BACKGROUND

Spina bifida, the most common neural tube defect (NTD), carries enormous medical, quality of life, and financial burdens (Botto, Moore, Khoury, & Erickson, 1999; Mitchell et al., 2004). Failure of the neural tube to close around the fourth week of embryonic development results in exposure of the spinal cord and its meninges through a gap in the spine, often leading to paralysis and other complications (Northrup & Volcik, 2000). Known risk factors for spina bifida include family history, maternal pregestational diabetes, obesity, lower socioeconomic status, hyperthermia, and exposure to certain medications such as valproate (Agopian, Tinker, Lupo, Canfield, & Mitchell, 2013; Avagliano et al., 2018). Given a protective effect of maternal periconceptional folic acid use against NTDs, the U.S. Public Health Service in 1992 recommended that all women of childbearing age consume at least 400 mcg of folic acid per day (MMWR Recomm Rep, 1992), and in 1998, folic acid fortification of enriched cereal grain products was mandated in the United States. Although rates of spina bifida have fallen substantially since 1998 (MMWR Recomm Rep, 1992), over 1,600 births continue to be affected annually in the United States (Williams et al., 2015).

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, aspirin, naproxen, and cyclooxygenase-2 (COX2) inhibitors, are among the medications used most commonly during pregnancy (Mitchell et al., 2011; Werler, Mitchell, Hernandez-Diaz, & Honein, 2005). Indicated for a variety of ailments, NSAIDs block COX enzymes and reduce prostaglandins with the effect of reducing pain, fever, and inflammation (Davis et al., 2017). Human data concerning the relation between periconceptional use of NSAIDs and the risk of spina bifida are limited, but two analyses from the National Birth Defects Prevention Study (NBDPS) identified an adjusted odds ratio (aOR) of 1.5 (95% confidence interval [CI] [1.2, 1.8]) for periconceptional use of any NSAID (Interrante et al., 2017) and aORs of 1.6 for both aspirin (95% CI [0.9, 2.7]) and ibuprofen (95% CI [1.2, 2.1]) when specific NSAIDS were considered (Hernandez, Werler, Romitti, Sun, & Anderka, 2012). A case–control study in Hungary looked at NSAID use later in the first trimester (5th through 12th week) in association with spina bifida or other NTD and reported an aOR of 1.1 (95% CI [0.7, 1.6]; Nørgård, Puhó, Czeizel, Skriver, & Sørensen, 2005). Other studies have lacked statistical power due to insufficient numbers of exposed cases (Ofori, Oraichi, Blais, Rey, & Bérard, 2006; van Gelder, Roeleveld, & Nordeng, 2011).

The aim of this study was to assess the relationship between maternal NSAID use in the periconceptional period and spina bifida, and to assess whether folic acid intake modifies the association.

2 | METHODS

This analysis used data from the Slone Epidemiology Center Birth Defects Study (Slone BDS), a multicenter case–control study that includes interview data from over 50,000 mothers of infants with and without birth defects between 1976 and 2015. The analysis was restricted to 1998–2015, the years after folic acid fortification was implemented in the United States. Subjects during that period were identified from participating hospitals in the greater metropolitan areas of Boston, Massachusetts; Philadelphia, Pennsylvania; Toronto, Canada; San Diego, California; and Nashville, Tennessee as well as via birth registries from Massachusetts and New York State. Study subjects were identified through review of admissions and discharges at major pediatric referral hospitals and clinics, at birth hospitals, and in logbooks in neonatal intensive care units; through weekly telephone contact with collaborators at newborn nurseries in community hospitals; and through collaborations with state birth defects registries. Detailed descriptions of the study methods have been previously described (Louik, Lin, Werler, Hernández-Díaz, & Mitchell, 2007; Mitchell et al., 2011; Werler, Hayes, Louik, Shapiro, & Mitchell, 1999).

Mothers were interviewed within 6 months of delivery by trained study nurses using a computer-assisted interview. Interviews included questions on a variety of demographic and clinical characteristics such as age, race and ethnicity, education, income, marital status, parity, whether the pregnancy was planned, height, and weight. Mothers were also asked about folic acid intake via an adapted Willett food frequency questionnaire focusing on the 6 months prior to pregnancy and use of supplements (e.g., prenatal vitamins). For this analysis, intakes of folic acid from supplements within 1 month before and after the LMP and diet were combined. Dietary values of folic acid and folate were adjusted for total energy intake and natural folate from diet was discounted by 30% given lower bioavailability, as has been previously described (Kerr, Parker, Mitchell, Tinker, & Werler, 2017; Parker, Yazdy, Tinker, Mitchell, & Werler, 2013). Individuals were then categorized as receiving adequate or inadequate folic acid intake based on a cut-point of 400 mcg/day. Exposures to prescription and over the counter medications were identified based on self-report with prompts based on illness, medication category, symptoms, and specific drugs to encourage comprehensive reporting. Dose, indication, timing, and certainty about timing were captured for all reported exposures. Mothers were asked to retrieve the bottle or package for reported medications, if available, to confirm the dose. Further, a booklet containing pictures of a wide range of over the counter medications was provided to mothers for use during the interview to assist in identification of medications.

The current study was restricted to live-born singleton infants born either with spina bifida (cases) or without major malformations (controls). Data for Slone BDS were collected for a variety of malformations across multiple geographic areas. To ensure that controls represented the populations that gave rise to the spina bifida cases included in this analysis, the population was restricted to individuals identified from hospitals from which both spina bifida cases and controls were ascertained. Infants affected by chromosomal anomalies, known syndromes, amniotic bands, or body wall defects were excluded.

For this analysis, the main exposure of interest was use of NSAIDS, specifically aspirin, ibuprofen, naproxen, and COX2 inhibitors, individually or in combination products, within 1 month (28 days) before or after the first day of the last menstrual period (LMP). This "periconceptional" exposure time frame was selected because it is the critical period for development of spina bifida (Botto et al., 1999; Mitchell et al., 2004; Northrup & Volcik, 2000). Exposed mothers were compared to mothers with no reported NSAID use during the same time frame; mothers whose timing of NSAID use was unknown were excluded. Because of possible misclassification of exposure timing, we performed sensitivity analyses that explored alternative exposure windows (2 months before LMP through 2 months after LMP and 0 months before through 3 months after LMP). Additionally, other pain medications, specifically opioid analgesics and acetaminophen regardless of concomitant NSAID use, were identified in the periconceptional interval. These medications were considered as candidates for confounder adjustment and were used as alternative exposures in sensitivity analyses.

Cases and controls were compared with respect to baseline demographic and clinical characteristics identified from the questionnaire and based on their periconceptional NSAID exposure. Odds ratios (ORs) and their 95% CIs were then calculated using logistic regression. In addition to unadjusted (crude) analyses, we assessed race/ethnicity, pregnancy intention, study center, body mass index, tobacco use, diabetes, periconceptional use of opioid analgesics, periconceptional use of acetaminophen, periconceptional use of valproate, calendar year, family history of NTDs, and education for inclusion as covariates in adjusted models based on whether removal of each variable from the full model changed OR estimates by more than 10%. Based on these criteria, race/ethnicity and study center were retained in the final adjusted models. In additional analyses, models were stratified based on whether the mother reported an average daily folic acid intake <400 mcg or ≥400 mcg in order to assess whether any risk associated with NSAID use is modified by folic acid intake. ORs were also estimated according to race/ethnicity for NSAIDs overall and NSAID exposure modified by folic acid intake. In a sub-analysis, NSAID exposure was compared between controls and cases, according to whether additional malformations were present (isolated and multiple cases). Analyses were performed using SAS Enterprise Guide version 7.15 (SAS Institute, Cary, NC). Approval from the Boston University Institutional Review Board was granted prior to conduct of the study.

3 | RESULTS

Of the 436 potential spina bifida cases identified in Slone BDS between 1998 and 2015, 62 were ineligible based on the results of medical record review. Of the 374 qualifying cases, 267 (71.3%) were included in the analysis after exclusion of 47 mothers with unknown timing of NSAID exposure, 7 multiple births, and 53 case infants recruited from settings with no appropriate controls. There were 191 (71.5%) isolated spina bifida cases and 76 (28.5%) cases with multiple malformations including spina bifida included in the analyses. Of 10,269 controls, 6,233 (60.7%) were retained after exclusion of 1,497 mothers with unknown timing of periconceptional NSAID exposure, 155 multiple births, and 2,384 recruited from settings with no included cases (Figure 1).

Compared with mothers of controls, mothers of cases were similar in age but more often Hispanic (26.2 vs. 20.2%) and less often non-Hispanic White (55.1 vs. 60.7%). A lower proportion of mothers of cases were married (44.9 vs. 49.2%), had education beyond high school (31.5 vs. 49.1%), or reported that the pregnancy was planned (38.2 vs. 43.1%). History of smoking was more common among mothers of cases (18.4 vs. 13.4%), as was obesity (22.5 vs. 13.2%). There were also differences by study center and year of LMP. An average daily dose of folic acid under 400 mcg was reported by 52.8% of case mothers and 46.2% of control mothers (Table 1).

Periconceptional exposure to any NSAID was reported by 22.9 and 20.2% of case and control mothers, respectively. Ibuprofen was the most commonly reported NSAID, reported by 18.4% of case mothers and 15.8% of control mothers, followed by aspirin (4.5 and 4.1%, respectively), and naproxen (3.4 and 2.5%, respectively). COX2 exposure was rare (no exposed case mothers and five exposed control mothers). Exposure to multiple different NSAID products during the exposure window was reported by 2.3% of case mothers and 1.3% of control mothers (data not shown). Among controls, mothers who were exposed to at least one NSAID (compared to mothers with no NSAID exposure) more often were non-Hispanic White (72.6 vs. 57.8%), smoked (19.0 vs. 11.9%) and consumed an average daily dose of folate of <400 mcg (57.4 vs. 50.4%; Table 1).

Compared to no NSAID use during the periconceptional period, use of any NSAID was associated with a modestly increased risk for spina bifida (aOR: 1.35, 95% CI [1.00, 1.83]; Figure 2). The aOR for ibuprofen was 1.42 (1.03, 1.97); for aspirin, it was 1.21 (0.66, 2.20), and for naproxen 1.53 (0.76, 3.08); for all estimates, lower 95% confidence bounds were less than or included 1.0. The strongest aOR was observed for multiple NSAID exposure (aOR 2.05; 95% CI [0.87, 4.83]), but the estimate was imprecise, given only six exposed and eight unexposed mothers. Adjusted estimates showed a slightly stronger association than unadjusted estimates. Due to a lack of exposed case mothers, associations with COX2 exposure could not be estimated.

In analyses stratified by folic acid use (Figure 3), associations with spina bifida were observed only for mothers with folic acid intake <400 mcg for any NSAID (aOR: 1.70, 95% CI [1.13, 2.57]), ibuprofen (aOR: 1.83; 95% CI [1.17, 2.86]), and naproxen (aOR: 2.33; 95% CI [1.02, 5.33]). For mothers with intake ≥400 mcg/day, aORs for any NSAID and all specific NSAIDS approximated 1 or lower; the same pattern of effect modification was observed for the multiple NSAID group, though the aOR for higher intake was 1.35, with wide confidence bounds. As was observed for the overall associations, aORs were greater than their unadjusted counterparts (data not shown).

Considering subgroups based on race/ethnicity, we saw a larger association between NSAID use and spina bifida for black women, and a weaker association for Hispanic women. Modification by folic acid had the largest impact in White women (study center adjusted OR 1.62, 95% CI [0.95, 2.73] with low FA, 1.08, 95% CI [0.67, 1.74] with high FA), a similar but weaker impact with poor precision in Hispanic women (study center adjusted OR 1.39, 95% CI [0.63, 3.07] with low FA, 0.93, 95% CI [0.30, 2.87] with high FA), and little impact

with poor precision in black women (study center adjusted OR 2.13, 95% CI [0.36, 12.46] with low FA, 1.84, 95% CI [0.64, 5.31] with high FA).

When restricting the cases to individuals with isolated spina bifida, we also saw a slightly larger association between NSAID use and spina bifida than was observed in the overall study population (aOR 1.49, 95% CI [1.06, 2.10]). Conversely, analyses limited to cases with multiple defects including spina bifida did not suggest an association with NSAID use (aOR 1.05, 95% CI [0.58, 1.90]).

Sensitivity analyses evaluating broader exposure windows were similar in direction and impact after adjusting for confounding. For use of other pain medications, acetaminophen was not associated with spina bifida overall (aOR 1.03, 95% CI [0.75, 1.41], Figure 2) or in folic acid-specific strata (aOR 0.83, 95% CI [0.51, 1.33] for <400 mcg of folic acid per day, 1.26, 95% CI [0.80, 1.99] for ≥400 mcg of folic acid per day, Figure 3). The OR for overall opioid use was elevated (aOR 2.23, 95% CI [1.09 4.57], Figure 2), consistent with prior analyses of the data set (Yazdy, Mitchell, Tinker, Parker, & Werler, 2013). As was observed for NSAIDS, the OR for opioids was elevated among those using <400 mcg of folic acid per day (aOR 3.22, 95% CI [1.19, 8.75], Figure 3) more than for those with sufficient intake (aOR 1.23, 95% CI [0.38, 4.21], Figure 3). Although there was some overlapping use of opioids and NSAIDs, the relation between NSAID use and spina bifida was not meaningfully different when adjusting for opioid use.

4 | DISCUSSION

Although the U. S. Food and Drug Administration (FDA) recommends that pain medications including NSAIDs, acetaminophen, and opioids be used only with caution during pregnancy (Research C for DE and FDA, 2019), they are among the most commonly-used medications during this time. We observed a small increase in the odds of spina bifida among infants born to periconceptional NSAID users, which is consistent with associations of similar magnitude observed in previous research (Hernandez et al., 2012; Interrante et al., 2017). Of importance, we further observed that the association appears limited to mothers with folic acid intake that is inadequate for NTD prevention; the same apparent effect modification was observed for use of opioid analgesic medications.

The biologic plausibility of folic acid exposure as a modifier of the association between NSAIDs and spina bifida is supported by animal models, which show the anti-inflammatory activity of NSAIDS occurs in part via inhibition of folate-dependent enzymes (Baggott, Morgan, Ha, Vaughn, & Hine, 1992). In addition, cardiotoxicity of the NSAID celecoxib appeared to be reduced by folic acid in rodents (Ahmad, Panda, Kohli, Fahim, & Dubey, 2017). Given the role of folic acid in prevention of NTDs, possible inhibition of its protective effects via NSAID use may have population-level implications, underscoring the importance of consuming the recommended amount of folic acid before and during pregnancy.

Several strengths support study validity. Outcomes were identified using a rigorous process based on clinical data, with review by a clinical geneticist to support final classification

(Parker, Yazdy, Mitchell, Demmer, & Werler, 2014). Definitions of folic acid use considered both dietary sources and supplements, yielding a more complete assessment of this key variable than is typically provided by definitions relying on supplements alone, noting that differences in bioavailability of folate across sources and inaccuracies in self-reported dietary intake do allow for potential misclassification. Although exposure and covariate variables were based on self-report, measures were taken to minimize misclassification. The specific interviewing techniques and questionnaire design used in the Slone BDS study, such as four-stage prompting, an interval between birth and data collection not longer than 6 months, and use of aids such as pill bottles and medication images, were designed to enhance accuracy in medication recall and applied equally to cases and controls. While it is theoretically possible that misclassification of exposure could explain the observed elevation in the odds of spina bifida among those with low folic acid status, nondifferential misclassification would create the expectation of a bias toward rather than away from the null, indicating that the observed result would be an underestimate of the true association. Further, analyses that varied the exposure window were not meaningfully different from the main analysis. We believe it is unlikely that recall bias explains our observed findings. For the observed increased ORs to have an upward bias among women with low FA intake, the degree of differential misclassification would need to be severe. For example, if mothers of cases were perfect reporters, 20% of control mothers would need to fail to report true exposure. Although increased recall that tends toward over-reporting (and thus false positive exposure reports) is possible, we have found no instances where women reported exposure to a fictitious drug (Parks, Canfield, & Ramadhani, 2011); neither scenario seems likely in terms of the required degree of misclassification.

Our analysis was unable to fully account for potential confounding by indication. NSAIDs are widely used to treat symptoms of a variety of illnesses and conditions that may cause fever, which is itself associated with an increased spina bifida risk. A recent study of Slone BDS data showed a positive association between maternal periconceptional fever and an increased risk for NTDs (OR: 2.4; 95% CI [1.5, 4.0]) with an attenuated association for mothers who reported adequate folic acid consumption (Werler et al., 1999). However, the null finding for acetaminophen, which is used for many of the same indications as NSAIDs, including fever, suggests that confounding by fever is unlikely to fully account for study findings.

Restriction to live births could bias study results because an estimated 12% of pregnancies affected by spina bifida end in fetal death or induced abortion (Parks et al., 2011). If NSAID use was associated with spina bifida- affected pregnancies ending in nonlive births, our results would underestimate true increased risks [Ahmad, Panda, Kohli, Fahim, & Dubey, 2017]). Potential cases and controls who were excluded due to other criteria were also more often White, married, and more highly educated than their included counterparts. Given that more controls than cases were excluded, and that study inclusion relies on voluntary participation, there is some potential for selection bias to impact study results.

We were constrained by sample size limitations, resulting in imprecision of some OR estimates, an inability to assess risk of COX2 inhibitors, and limited power to explore the role of concomitant use of either multiple NSAIDs or concomitant use of NSAIDs and

opioid analgesics. The numbers of Hispanic and black women in the study were small, resulting in unstable ORs estimates.

In summary, our results underscore the importance of adequate folic acid intake in prevention of spina bifida, which may be particularly important for mothers with periconceptional use of NSAID medications.

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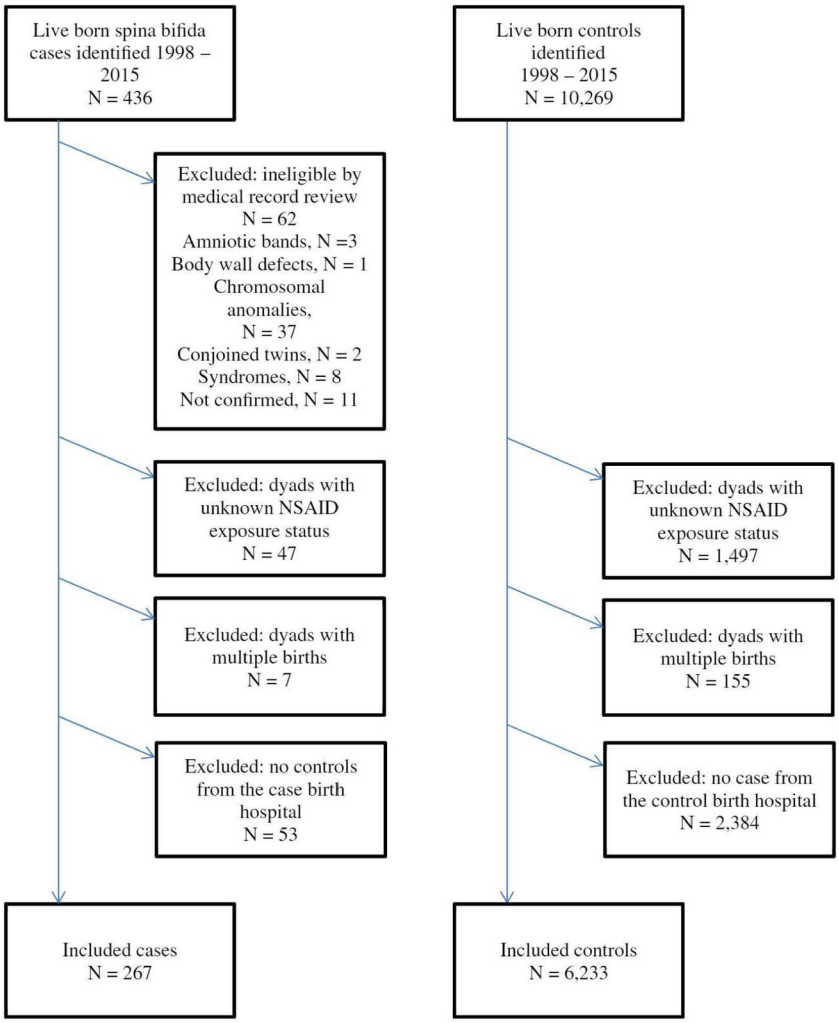

FIGURE 1.
Formation of the study population

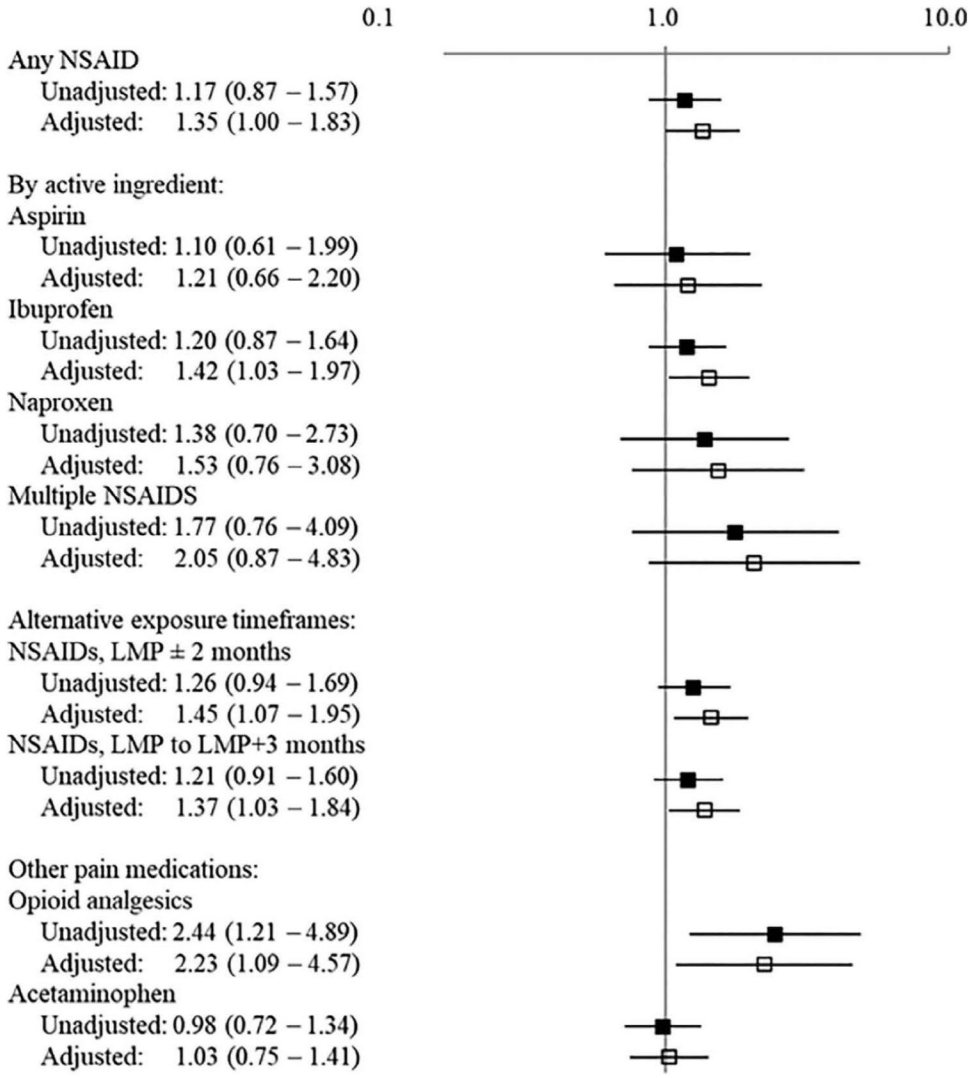

FIGURE 2.

Unadjusted and adjusted odds ratios of spina bifida for nonsteroidal anti-inflammatory drug (NSAID) exposed versus unexposed mothers

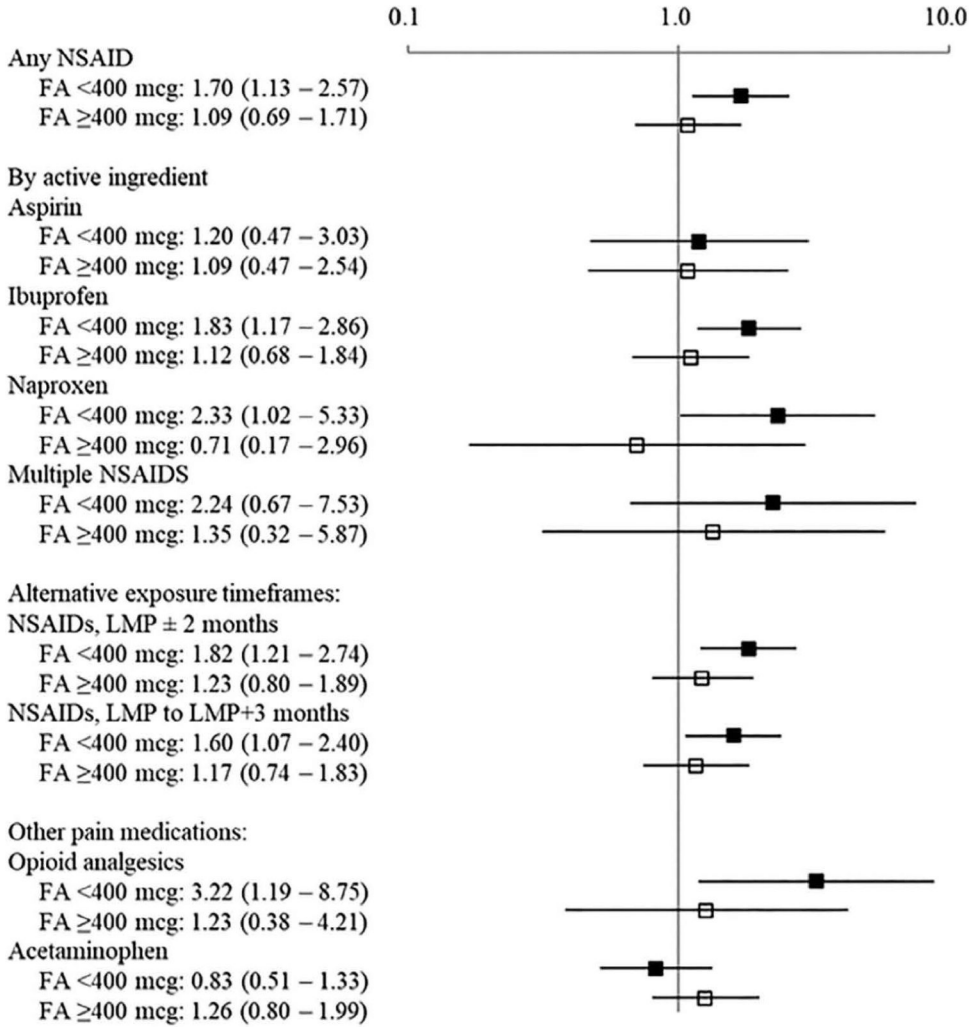

FIGURE 3.

Adjusted odds ratios of spina bifida for nonsteroidal anti-inflammatory drug (NSAID) exposed versus unexposed mothers stratified by average daily folic acid (FA) intake

TABLE 1

Characteristics of live born spina bifida cases and controls, Slone Epidemiology Center Birth Defects Study, 1998–2015

	Cases		Controls					
			All		NSAID exposed		Unexposed	
	N	%	*N*	%	*N*	%	*N*	%
Total	267	100.0	6,233	100.0	1,257	100.0	4,976	100.0
Maternal age (years)								
Under 18	9	3.4	204	3.3	28	2.2	176	3.5
18–24	62	23.2	1,245	20.0	227	18.1	1,018	20.5
25–34	159	59.6	3,696	59.3	781	62.1	2,915	58.6
35 and older	37	13.9	1,088	17.5	221	17.6	867	17.4
Race and ethnicity								
Non-Hispanic White	147	55.1	3,786	60.7	912	72.6	2,874	57.8
Non-Hispanic black	26	9.7	599	9.6	85	6.8	514	10.3
Hispanic	70	26.2	1,257	20.2	197	15.7	1,060	21.3
Other	24	9.0	591	9.5	63	5.0	528	10.6
Body mass index								
Under 18.5	8	3.0	272	4.4	42	3.3	230	4.6
18.5–24.9	122	45.7	3,714	59.6	763	60.7	2,951	59.3
25.0–29.9	65	24.3	1,242	19.9	247	19.7	995	20.0
30 or more	60	22.5	825	13.2	189	15.0	636	12.8
Unknown	12	4.5	180	2.9	16	1.3	164	3.3
Married	120	44.9	3,068	49.2	660	52.5	2,408	48.4
Maternal education								
Less than high school	49	18.4	647	10.4	98	7.8	549	11.0
Completed high school	134	50.2	2,523	40.5	500	39.8	2,023	40.7
More than high school	84	31.5	3,057	49.1	659	52.4	2,398	48.2
Unknown	0	0.0	6	0.1	0	0.0	6	0.1
Pregnancy planned	102	38.2	2,685	43.1	549	43.7	2,136	42.9
Smoking history	49	18.4	832	13.4	239	19.0	593	11.9
Family history of neural tube defects	7	2.62	55	0.9	8	0.8	47	0.9

	Cases		Controls					
			All		NSAID exposed		Unexposed	
	N	%	*N*	%	*N*	%	*N*	%
Study center								
Boston	50	18.7	2,302	36.9	561	44.6	1,741	35.0
Philadelphia	60	22.5	1,534	24.6	281	22.4	1,253	25.2
Toronto	55	20.6	358	5.7	59	4.7	299	6.0
San Diego	46	17.2	1,445	23.2	252	20.1	1,193	24.0
New York	43	16.1	492	7.9	89	7.1	403	8.1
Tennessee	13	4.9	102	1.6	15	1.2	87	1.8
Year of LMP								
1997–2001	72	27.0	1,759	28.2	379	30.2	1,380	27.7
2002–2007	75	28.1	1,373	22.0	361	28.7	1,317	26.5
2008–2014	77	28.8	2,051	32.9	517	41.2	2,279	45.8
Folic acid intake								
≥400 mcg/day	117	43.8	3,231	51.8	521	41.5	2,361	47.5
<400 mcg/day	141	52.8	2,882	46.2	721	57.4	2,510	50.4
Unknown	9	3.4	120	1.9	15	1.2	105	2.1
Use of medications								
Any NSAID	61	22.9	1,257	20.2	1,257	100.0	0	0.0
Aspirin	12	4.5	256	4.1	256	20.4	0	0.0
Ibuprofen	49	18.4	987	15.8	987	78.5	0	0.0
Naproxen	9	3.4	154	2.5	154	12.3	0	0.0
COX 2 inhibitors	0	0.0	5	0.1	2	0.2	0	0.0
Acetaminophen	54	20.2	1,290	20.7	468	37.2	822	16.5
Opioid analgesics	9	3.4	88	1.4	32	2.6	56	1.1
Valproate	0	0.0	6	0.1	2	0.2	4	0.1