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Is There Etiologic Heterogeneity between Upper and Lower Neural Tube Defects?

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Neural tube defects are thought to arise from two different embryologic mechanisms depending on the level of the defect: neurulation defects associated with anencephaly and upper spina bifida and canalization defects associated with lower spina bifida. To investigate whether the risk profiles of neural tube defect cases differ according to the level of the defect, the authors examined data from the Atlanta Birth Defects Case-Control Study. Cases were infants live- or stillborn from 1968 to 1980 with these defects, and controls were infants without defects randomly selected and frequency matched to cases by race, birth year, and hospital of birth. By multivariate polychotomous logistic regression, 1,186 controls were compared with cases: 145 with anencephaly, 59 with upper spina bifida (cervical/thoracic lesions), and 100 with lower spina bifida (lumbar/sacral lesions). Infant's sex and sibling recurrence of neural tube defects were the only factors for which the case subgroups significantly differed in risk. The risks associated with selected maternal exposures during the first trimester of pregnancy did not differ among the case subgroups. Although these results do not support the concept that upper and lower neural tube defects differ in risks from exogenous factors, differences in sibling recurrence and in risks by sex between the two groups suggest an underlying heterogeneity in genetic susceptibility factors. *Am J Epidemiol* 1992;136:1493–1501.

anencephaly; case-control studies; neural tube defects; spina bifida

Anencephaly and spina bifida are defects of the central nervous system that result from a failure in the closure of the neural tube. Developmental evidence indicates that two distinct processes are involved in the formation of the neural tube, neurulation and canalization (1–4). Neurulation is characterized by the folding of the neural plate, which fuses at the midline to form the neural tube. Canalization describes a subsequent process in which vacuoles within a mass of undifferentiated cells coalesce to form a lumen and connect with the previously formed neural tube.

The posterior neuropore is considered to be the junction between where neurulation occurs and where canalization occurs, and its precise location appears to vary among human embryos. The vertebral level for this junction has been suggested to be as high as thoracic 11 and as low as sacral 2 (1, 2, 4–6). Neural tube defects above the posterior neuropore may be caused by a fault in neurulation, and those below may be caused by a fault in canalization, thereby being etiologically distinct from one another.

Because neurulation and canalization de-

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Abbreviation: CI, confidence interval

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fects are not easily defined pathologically, the level of the lesion is used as a surrogate measure to define the two groups. Evidence suggests that cases with upper and lower neural tube defects, separated at the vertebral level thoracic 11/12, differ in sex ratio, in recurrence of neural tube defects among siblings, and in the cooccurrence of other defects (7–12). However, the possibility that suspected exogenous exposures may differentially affect high and low neural tube defects has not been examined in case-control studies.

Our study is the first population-based case-control study designed to evaluate whether there is etiologic heterogeneity among neural tube defects divided according to the level of the lesion. The cases were separated into three groups by defect level, anencephaly, upper spina bifida (cervical/thoracic lesions), and lower spina bifida (lumbar/sacral lesions), and they were simultaneously compared with a population control group without birth defects to determine whether the risk profiles of the three case subgroups differed.

MATERIALS AND METHODS

Data for this study were collected as part of the Atlanta Birth Defects Case-Control Study conducted from 1982 through 1984. In this study, information was collected through a computer-assisted telephone interview with mothers of case and control infants. Case infants with serious malformations were identified from the Metropolitan Atlanta Congenital Defects Program, which is a population-based surveillance system in the five-county metropolitan Atlanta area. The Metropolitan Atlanta Congenital Defects Program registry uses multiple sources of ascertainment, and because of the comprehensive follow-up, its case ascertainment is considered essentially complete. The details of the methodology for the Atlanta Birth Defects Case-Control Study and Metropolitan Atlanta Congenital Defects Program are published elsewhere (13, 14).

Cases for the current investigation were infants with anencephaly, spina bifida, or both, who were live-born or stillborn between 1968 and 1980 in the Metropolitan Atlanta Congenital Defects Program surveillance area and whose mothers participated in the Atlanta Birth Defects Case-Control Study telephone interview. Of the 519 cases registered in the Metropolitan Atlanta Congenital Defects Program, 341 (65.7 percent) participated in the Atlanta Birth Defects Case-Control Study.

Controls were live-born infants without birth defects who were randomly selected from all infants born alive in the Metropolitan Atlanta Congenital Defects Program surveillance area between 1968 and 1980 and whose mothers participated in the Atlanta Birth Defects Case-Control Study. The control group of 1,186 infants was frequency matched to the case group by year and quarter of birth, race, and hospital of birth. The participation rate among controls was 71.3 percent.

We reviewed medical records of the cases to obtain information on the level of the defect and on whether the lesion was open or closed (i.e., whether the neural tissue was exposed or not). Information on the uppermost vertebral level of the neural tube defect lesion along with the diagnostic source of information was abstracted. When discrepancies existed between different sources of information on the level of the defect recorded for the same infant, the source deemed most accurate was used. The order of priority was radiographic examination report, autopsy report, surgery report, discharge diagnosis, consultation note, and admission diagnosis. Thus, for example, if a radiographic examination report was not available and the surgery report noted that the lesion was in the low thoracic area but that the discharge diagnosis was recorded as "lumbar spina bifida," then we assigned the uppermost vertebral level as "thoracic." Radiographic examination reports, denoting the exact vertebral location of the neural tube defect, were available on 41 percent of the spina bifida cases.

For analysis, spina bifida cases were divided into two groups: upper spina bifida

cases and lower spina bifida cases. Upper spina bifida cases involved lesions starting in the cervical or thoracic region; lower spina bifida cases involved lesions starting in the lumbar or sacral area. Of the 341 cases, 145 had anencephaly, 59 had upper spina bifida, and 100 had lower spina bifida. The location of the neural tube lesion in the remaining 37 cases was unknown.

Data on infants listed in the Metropolitan Atlanta Congenital Defects Program registry included sex, race, date of birth, hospital of birth, and whether they had other unrelated major defects. Mothers were questioned about their age at infant's birth, education, pregnancy history (including birth defects in other children), and exposure to acute illnesses, drugs, cigarette smoking, alcohol, and beverages containing caffeine during pregnancy.

Data analysis was performed by using polychotomous logistic regression to simultaneously compare the case subgroups with the control group while controlling for the effects of confounding variables. Polychotomous logistic regression allowed estimation of the subgroup-specific risk parameters and direct statistical significance testing of the null association between each parameter and the defect subtype (15, 16). To test the difference in odds ratios between the case subgroups, χ^2 statistics for comparing two dependent samples (17) were used. For multivariate modeling, variables significantly associated with dependent outcomes and those considered to be confounders in previous studies were included in the final model. These confounders were the infant's year of birth, race, and birth order and the mother's education and age at the infant's birth.

RESULTS

Of the 304 cases whose level of the lesion was known, 47.7, 19.4, and 32.9 percent had anencephaly, upper spina bifida, and lower spina bifida, respectively. Characteristics of the study participants are shown in table 1. The proportion of male infants varied among case subgroups: 35.9, 40.7, 49.0, and 56.8 percent, respectively, for the anencephaly, upper spina bifida, and lower spina bifida subgroups and for the subgroup with unclassified spina bifida, in comparison with 51.4 percent male in the control group. The risks of neural tube defects among siblings significantly differed among the subgroups; they were 1.29, 2.26, and 0.09 percent for the anencephaly, upper spina bifida, and control groups, respectively. No instances of siblings with neural tube defects were reported during the study period among infants with lower spina bifida or unclassified neural tube defects. The frequency of other major birth defects, not secondary to neural tube defects, also varied among case subgroups, but this difference was not statistically significant. The case subgroups did not differ significantly in the infants' birth order or in the mothers' education or age at index birth. Mothers of infants with an unknown level of spina bifida exhibited characteristics that were somewhat different from those of other mothers; i.e., they were more likely to be older at the time of the index birth and to have a lower educational level.

Odds ratios associated with the mother's exposures during the first trimester of pregnancy, adjusted for race and birth year, are displayed in table 2. The risk patterns of maternal exposures were similar for all three case subgroups. Periconceptional vitamin use was inversely associated with case status but was only marginally significant; the odds ratios were near 0.5 for all three case subgroups. Maternal exposure to influenza was a significant risk factor for all case subgroups: odds ratios = 3.26 (95 percent confidence interval (CI) 1.59–6.65) for anencephaly, 4.57 (95 percent CI 1.81–11.53) for upper spina bifida, and 3.73 (95 percent CI 1.72–8.10) for lower spina bifida. Odds ratios close to one were obtained for smoking and alcohol drinking. We found no consistent risk pattern associated with the mother's daily caffeine intake from coffee, tea, or soda. When odds ratios were compared between the case subgroups, no significant differences were obtained for any exposure factors.

TABLE 1. Distribution of selected characteristics among cases with neural tube defects defined by defect level and among controls without birth defects: Atlanta, Georgia, 1968–1980

	Anencephaly		USB* (cervical/ thoracic)		LSB* (lumbar/ sacral)		SB* with unknown level		Control (no defect)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Total	145		59		100		37		1,186	
Male	52	35.86	24	40.68	49	49.00	21	56.76	610	51.43
Race, nonwhite	21	14.48	7	11.86	15	15.00	5	13.51	169	14.25
Born during										
1/68–4/72	64	44.14	31	52.54	30	30.00	22	59.46	477	40.22
5/72–8/76	38	26.21	14	23.73	38	38.00	7	18.92	354	29.85
9/76–12/80	43	29.66	14	23.73	32	32.00	8	21.62	355	29.93
Birth order										
1st	60	41.38	26	44.07	35	35.00	14	37.84	524	44.18
2nd	54	37.24	19	32.20	37	37.00	10	27.03	372	31.37
3rd	17	11.72	8	13.56	14	14.00	6	16.22	179	15.09
All others	14	9.66	6	10.17	14	14.00	7	18.92	111	9.36
Has other major defects	23	15.86	17	28.81	22	22.00	6	16.22	(Not applicable)	
Has sibling with NTD*,†	5	1.29	3	2.26	0	0.00	0	0.00	2	0.09
Mother's age at birth (years)										
11–19	19	13.10	6	10.17	9	9.00	2	5.41	108	9.11
20–34	115	79.31	52	88.14	84	84.00	30	81.08	1,025	86.42
≥35	11	7.59	1	1.69	7	7.00	5	13.51	53	4.47
Mother completed										
Grammar school	28	19.31	9	15.25	16	16.00	10	27.03	164	13.83
High school	94	64.83	42	71.19	65	65.00	23	62.16	788	66.44
Some college or more	23	15.86	8	13.56	19	19.00	4	10.81	234	19.73

* USB, upper spina bifida; LSB, lower spina bifida, SB, spina bifida, NTD, neural tube defect.
† Numbers of all siblings, live-born and stillborn up to 1982–1983, are 388, 133, 207, 97, and 2,350 for infants with anencephaly, USB, LSB, SB with unknown level, and without defects, respectively.

Results of the multivariate analysis were similar to those of univariate analyses (table 3). No variable had any significant effects on the risk estimates of any other variables in the multivariate model. None of the possible confounders showed a significant relation with the defect status nor did they affect the case subgroups in a significantly different manner. Variables for which odds ratios significantly differed between any two subgroups were infant's sex for anencephaly versus lower spina bifida and having a sibling with a neural tube defect for lower spina bifida versus either anencephaly or upper spina bifida. All case subgroups had significantly elevated risks associated with maternal exposure to influenza and marginally significant and reduced risks associated with periconceptional vitamin use.

DISCUSSION

This is the first population-based study to evaluate differences in risks among infants with neural tube defects subgrouped according to the level of the defect. Our study sample was relatively large compared with those of other studies. Our comprehensive and highly structured questionnaire and the computer-assisted telephone interviewing system we used resulted in the systematic collection of exposure information.

Although our results indicate that maternal exposure factors did not differ among the neural tube defect case subgroups, they suggest possible differences in genetic susceptibility among the subgroups. The finding that infants with anencephaly and upper spina bifida were more likely to be female

TABLE 2. Univariate odds ratios* associated with mother's exposure factors during the first trimester of pregnancy for anencephaly and spina bifida according to level of the lesion: Atlanta, Georgia, 1968–1980

	Anencephaly		USB† (cervical/thoracic)		LSB† (lumbar/sacral)		*p* values from χ^2 heterogeneity test		
	OR†	95% CI†	OR	95% CI	OR	95% CI	AE†/USB	AE/LSB	USB/LSB
Periconceptional vitamin									
No	1.00		1.00		1.00				
Yes (−3 to +3 months)	0.56	0.30–1.04	0.46	0.16–1.29	0.52	0.25–1.10	0.745	0.884	0.844
Influenza infection									
No	1.00		1.00		1.00				
Yes	3.26	1.59–6.65	4.57	1.81–11.5	3.73	1.72–8.10	0.529	0.774	0.718
Cigarette smoking									
Under one pack/day	1.00		1.00		1.00				
One pack or more/day	0.92	0.58–1.45	1.09	0.57–2.10	0.98	0.57–1.67	0.663	0.849	0.800
Alcohol drinking									
No	1.00		1.00		1.00				
Yes	0.80	0.56–1.14	0.87	0.51–1.48	1.13	0.75–1.71	0.803	0.190	0.426
Daily caffeine intake (mg)									
<250	1.00		1.00		1.00				
250–499	1.00	0.68–1.46	1.60	0.89–2.87	1.13	0.72–1.78	0.172	0.658	0.349
≥500	1.23	0.67–2.26	1.76	0.72–4.30	0.79	0.32–1.91	0.500	0.393	0.197

* Each odds ratio, based on case-control comparisons, is adjusted for race and birth year.
† USB, upper spina bifida; LSB, lower spina bifida; OR, odds ratio; CI, confidence interval; AE, anencephaly

and to have siblings with neural tube defects, but that those with lower spina bifida were not, is consistent with observations from other reports (7, 8, 10). In those studies, infants with neural tube defects were categorized as having a neural tube lesion above or below the vertebral level thoracic 11/12. Infants with anencephaly and upper spina bifida were predominantly female, whereas infants with lower spina bifida were nearly as likely to be male as female. Toriello and Higgins (10) reported a sibling recurrence of 4.2 percent for upper spina bifida and 2.8 percent for lower spina bifida, and Hall et al. (7) reported a sibling recurrence of 2.2, 7.8, and 0.7 percent, respectively, for anencephaly, upper spina bifida, and lower spina bifida.

The directions and magnitudes of the estimated risks we found for maternal exposure factors were also in agreement with those previously reported for anencephaly, spina bifida, or both. Influenza infection has been positively associated with anencephaly and spina bifida. The reported odds ratios range from 1.72 to 3.93 (18–21). Findings on the relation between neural tube defects and cigarette smoking had not been consistent, and elevated odds ratios for neural tube defects had only been found among women who smoked heavily (22–29). To date, most reports indicate that alcohol and caffeine intake are not risk factors for neural tube defects (30–33).

In more recent observational studies, periconceptional vitamin use was found to be protective against neural tube defects, the odds ratios ranging from 0.3 to 1.00 (34–37). Our estimated odds ratios for periconceptional vitamin use were higher and less significant than those reported in an earlier report (37), mainly because the categorization of "periconceptional vitamin exposure" was different. In the study by Mulinare et al. (37), "exposure" was defined as use of multivitamins or perinatal vitamins every month throughout the periconceptional period, and "nonexposure" was defined as not using any vitamins throughout this period. In our analysis, "exposure" was

TABLE 3. Multivariate odds ratios* for anencephaly and spina bifida cases subgrouped according to level of the lesion: Atlanta, Georgia, 1968–1980

	Anencephaly		USB† (cervical/thoracic)		LSB† (lumbar/sacral)		*p* values from χ^2 heterogeneity test		
	OR†	95% CI†	OR	95% CI	OR	95% CI	AE†/USB	AE/LSB	USB/LSB
Sex									
Female	1.00		1.00		1.00				
Male	0.51	0.34–0.75	0.59	0.33–1.06	0.90	0.58–1.39	0.643	0.045	0.251
Has sibling with NTD†									
No	1.00		1.00		1.00				
Yes	36.97	3.70–369	90.02	8.87–914	0.00		0.301	0.000	0.000
Birth order									
1st	1.00		1.00		1.00				
All others	1.21	0.80–1.83	1.05	0.57–1.93	1.56	0.96–2.54	0.699	0.407	0.303
Mother's age at birth (years)									
11–19	1.72	0.92–3.23	1.15	0.43–3.10	1.47	0.65–3.31	0.481	0.746	0.700
20–34	1.00		1.00		1.00				
≥35	2.16	1.00–4.68	0.58	0.08–4.37	1.36	0.51–3.61	0.222	0.433	0.446
Mother's education‡	0.87	0.62–1.21	0.81	0.48–1.37	0.99	0.67–1.47	0.833	0.580	0.529
First trimester influenza									
No	1.00		1.00		1.00				
Yes	3.56	1.72–7.40	3.98	1.45–10.9	4.18	1.90–9.23	0.849	0.739	0.934
Periconceptional vitamin									
No	1.00		1.00		1.00				
Yes	0.58	0.30–1.13	0.52	0.18–1.53	0.49	0.22–1.10	0.855	0.737	0.930

* Each odds ratio, based on case-control comparisons, is adjusted for race, birth year, and all other variables.
† USB, upper spina bifida; LSB, lower spina bifida; OR, odds ratio; CI, confidence interval; AE, anencephaly; NTD, neural tube defect.
‡ Treated as a continuous variable of three values: 1 = completed grammar school, 2 = completed high school, and 3 = attended college.

defined the same, but "nonexposure" was defined as no vitamin use, early or late postconceptional vitamin use, and other vitamin use.

Our study findings imply that the agents examined in this study have similar effects on the closure of the neural tube regardless of the level. Caution must be taken in interpreting these results though. Misclassification might be responsible for our finding that external exposure risks did not vary significantly by defect level. In other words, the thoracic/lumbar junction may not be the correct level that distinguishes neurulation from canalization. Perhaps the true dividing point is sacral 2/3 as suggested by Muller and O'Rahilly (4). However, categorizing cases above or below this level was not feasible in our study, because there were virtually no cases involving lesions below sacral 2 in our study group.

We did, however, explore an alternative classification scheme, based on the developmental theory of Lemire. He suggested that neural tube defects arising after neurulation are skin covered, because the embryonic ectoderm covers the surface of the embryo after the posterior neuropore closes (38, 39). Following this theory, we considered defects involving lumbar/sacral spina bifida in which the lesion was skin covered (or closed) to be canalization defects ($n = 24$), and we considered the rest of the defects to be neurulation defects (anencephaly, $n = 145$; upper spina bifida, $n = 131$). A comparison of neural tube defect cases classified according to this system revealed that lumbosacral spina bifida involving a closed lesion displayed a somewhat different risk profile than that of the other neural tube defects (table 4). For these cases, the only significantly associated factor was a birth order of two or lower. No mother in this group took periconceptional vitamins, and

TABLE 4. Multivariate odds ratios* for anencephaly and spina bifida cases subgrouped according to level and open/closed status of the lesion: Atlanta, Georgia, 1968–1980

	Anencephaly		USB† (cervical/thoracic/open lumbosacral spina bifida)		LSB† (closed lumbosacral spina bifida)		*p* values from χ^2 heterogeneity test		
	OR†	95% CI†	OR	95% CI	OR	95% CI	AE†/USB	AE/LSB	USB/LSB
Sex									
Female	1.00		1.00		1.00				
Male	0.50	0.34–0.74	0.72	0.49–1.06	1.15	0.49–2.70	0.182	0.083	0.324
Has sibling with NTD†									
No	1.00		1.00		1.00				
Yes	36.97	3.70–369	36.97	3.75–365	0.00		1.000	0.000	0.000
Birth order									
1st	1.00		1.00		1.00				
All others	1.20	0.79–1.81	1.08	0.71–1.64	4.63	1.34–16.03	0.707	0.041	0.028
Mother's age at birth (years)									
11–19	1.73	0.92–3.25	1.13	0.56–2.30	0.00		0.346	0.000	0.000
20–34	1.00		1.00		1.00				
≥35	2.17	1.00–4.71	1.20	0.45–3.18	0.87	0.11–6.79	0.315	0.405	0.778
Mother's education‡	0.87	0.62–1.22	0.80	0.56–1.15	1.29	0.61–2.74	0.744	0.333	0.252
First trimester influenza									
No	1.00		1.00		1.00				
Yes	3.52	1.70–7.29	4.80	2.45–9.41	1.96	0.25–15.4	0.472	0.589	0.405
Periconceptional vitamin									
No	1.00		1.00		1.00				
Yes	0.59	0.30–1.14	0.58	0.29–1.15	0.00		0.966	0.000	0.000

* Each odds ratio, based on case-control comparisons, is adjusted for race, birth year, and all other variables.
† USB, upper spina bifida; LSB, lower spina bifida; OR, odds ratio; CI, confidence interval; AE, anencephaly; NTD, neural tube defect.
‡ Treated as a continous variable of three values: 1 = completed grammar school, 2 = completed high school, and 3 = attended college.

the risk associated with influenza was not significantly elevated. Because of the small number of cases in this group, however, we had difficulty determining whether such seemingly different risks were real or due to unstable estimation.

Also examined in our analysis was whether isolated neural tube defects (without other major defects) and multiple neural tube defects (with other major defects) differed in risk patterns, because there are some suggestions that the two groups differ in epidemiologic characteristics (40–43). Our regression results indicated that the two groups did not differ significantly in any of the risk factors examined in this study other than the infant's sex. The risk of an isolated neural tube defect was lower among males than females (odds ratio = 0.58, 95 percent CI 0.43–0.78), although the risk of a multiple neural tube defect did not differ between males and females (odds ratio = 1.08, 95 percent CI 0.64–1.82). Also, when the isolated neural tube defect cases, which comprised the majority of our cases (80 percent), were subgrouped by the level of defect, their risks from maternal exposure factors did not differ by defect level.

Another factor contributing to misclassification may be inadequacies in the medical record information used to determine the specific level of the defect. Other than radiographic examination and autopsy reports, most other diagnostic sources only reported the general area of the skin defect. Certainly these sources cannot be expected to have the accuracy of the radiologic assessment of bone defect. In addition, clinicians tend to allot the skin defect to the level over which most of it lies (44). As a result, some thoracolumbar defects were probably misidentified as lumbar defects.

Other methodological limitations of the study include a relatively low participation rate and a possible recall bias. However, no clear evidence of selection bias or differential recall bias was seen. First, case and control mothers were remarkably similar in many demographic characteristics. Second, when a mother's exposure to other acute illnesses, excluding influenza, was examined, there were no differences in the proportion of case and control mothers reporting exposure. In addition, interviewer bias was avoided because the interviewers who collected exposure information did not know the case-control status of the mothers being interviewed.

An important issue in our study, however, is whether there was differential recall or participation by the level of the defect. Because both the upper and lower neural tube defects are serious defects, there is no reason to suspect that a differential recall or participation would have occurred by defect level. Furthermore, the observation that the risk estimates on the mother's various exposure factors did not differ by defect level reduces the possibility that a differential recall or participation by defect level has occurred.

A final limitation of this study is that cases included only live-born infants and stillborn fetuses whose gestational age was greater than 20 weeks; not included were fetuses that spontaneously aborted early in pregnancy. We do not believe that therapeutic abortion of fetuses with prenatally detected neural tube defects contributed to a selection bias in this investigation, because prenatal screening for neural tube defects had not been in general practice in Atlanta until the 1980s, nor would it have contributed to the decline in the number of cases born during the study period, as seen in table 1. The incidence of anencephaly and spina bifida has been consistently declining in Atlanta from 1968 through 1980 (41), for which the reasons are not clear. Virtually no data are available to compare the risk factors for spontaneously aborted neural tube defect cases with the risk factors for live-born and stillborn cases. Although these two groups may present similar risk profiles, we have no evidence that they do. On the other hand, the differences in risks by sex and in sibling recurrence seen between upper and lower neural tube defects may be a reflection of selective abortion in either group.

In summary, upper and lower neural tube defects divided at the thoracic/lumbar junction did not differ in risks from maternal exposure factors but possibly from genetic factors. This implies that, although these two defect subgroups may differ in genetic susceptibility, they may be affected similarly by environmental agents such as influenza infection, periconceptional vitamin use, cigarette smoking, and caffeine and alcohol consumption. When neural tube defect cases were grouped according to defect level and whether the lesion was open or closed, the risks associated with closed lumbosacral spina bifida appeared to differ from the risks associated with the other neural tube defects. However, the number of cases with closed lumbosacral spina bifida was too small to determine whether this difference was real or not. Further studies using improved classification methods are needed to verify these findings.

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