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Proportion of Neural Tube Defects Attributable to Known Risk Factors

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Abstract

BACKGROUND—Recognized risk factors for neural tube defects (NTDs) poorly predict population-level NTD risk. However, the proportion of NTDs that can be attributed to these risk factors is uncertain.

METHODS—To determine the proportion of NTD cases that is attributable to known or suspected risk factors (i.e., female infant sex, family history of NTDs, and maternal Hispanic ethnicity, obesity, pregestational diabetes, gestational diabetes, low dietary folate intake, lack of folic acid supplementation, anticonvulsant use, and hot tub or sauna use), we estimated the adjusted population attributable fraction (aAF) for each factor, using the method of Eide and Geffler and data from the National Birth Defects Prevention Study.

RESULTS—Our analyses of these data indicate that the proportion of cases of spina bifida and anencephaly that can be attributed to known risk factors is 28% and 44%, respectively. For spina bifida, the factor with the greatest attributable fraction was maternal obesity (aAF, 10%), whereas for anencephaly it was Hispanic ethnicity (aAF, 15%).

CONCLUSION—Our analyses indicate that known risk factors account for <50% of NTD cases. Hence, the majority of NTD cases are attributable to, as yet, unidentified factors. These findings highlight the need for continued research to identify genetic and additional nongenetic risk factors for NTDs. Further, these findings suggest that strategies that aim to reduce the risk of NTDs associated with maternal Hispanic ethnicity and obesity may have the greatest impact on the population prevalence of these conditions.

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INTRODUCTION

There are several factors that are known or highly suspected to increase the risk for neural tube defects (NTDs), including female infant sex and family history of NTDs, as well as maternal Hispanic ethnicity, obesity, folate status, pregestational diabetes, gestational diabetes, anticonvulsant use, and hot tub or sauna use (reviewed in Mitchell, 2005). Our previous work demonstrated that these factors poorly predict NTD risk at the population level (Agopian et al., 2012). However, the extent to which these factors account for the population burden of NTDs is unknown.

Population attributable fraction (AF), also known as etiologic fraction or attributable risk, is a measure that estimates the proportion of disease due to specific risk factors. Estimates of AFs can be used to prioritize public health interventions (e.g., by targeting the exposures responsible for the greatest burden of disease) and research efforts (e.g., by determining the proportion of disease risk that is unaccounted for). However, the assumptions that all risk factors act independently and are not influenced by confounders must be met for crude estimates of AF to be valid and these assumptions are not valid for complex diseases such as birth defects. Although methods for estimating AF that are adjusted for other variables (Eide and Gefeller, 1995; Eide, 2008; Rückinger et al., 2009) are available, they have not been widely used in birth defects research. An advantage of estimating adjusted AFs (aAFs) over crude AFs is that the sum of the aAFs for individual risk factors equals the estimated aAF for the combination of those risk factors. Further, because the total aAF (for all known and unknown risk factors) will equal 100%, the combined aAF of known risk factors can also be used to estimate the proportion of disease attributable to as yet unknown factors.

METHODS

Study Subjects

We used data from the National Birth Defects Prevention Study (NBDPS) to estimate aAFs for known NTD risk factors. The details of NBDPS subject recruitment and data collection methods have been previously described (Yoon et al., 2001). Briefly, data were collected from population-based surveillance systems located in 10 states: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. For the majority of surveillance sites (i.e., eight of the sites), cases included live births, fetal deaths, and elective pregnancy terminations. Abstracted medical records of cases were reviewed by NBDPS clinical geneticists to confirm diagnoses, evaluate the presence of additional birth defects, and exclude potential cases with single-gene disorders or chromosome abnormalities (Rasmussen et al., 2003). Live born controls without major birth defects were ascertained through birth certificate data or hospital birth logs. Controls were selected at random among infants delivered in the study regions. The institutional review boards for each study site approved the methods. Our analyses included NBDPS cases with spina bifida or anencephaly and control infants with due dates between October 1, 1997, and December 31, 2007. For these analyses, cases with additional major birth defects that were unlikely to be secondary to the NTD were excluded.

Risk Factors

Each participating mother completed a computer assisted telephone interview on exposures before and during pregnancy, including 10 known/highly suspected NTD risk factors: pre-pregnancy obesity (body mass index _30.0), pre-pregnancy (type I or II) diabetes, gestational diabetes, lack of any folic acid supplementation (folic acid, multivitamin, or prenatal supplement) during the month before pregnancy and the first month of pregnancy (B1_P1), low dietary folate intake (Agopian et al., 2012), anticonvulsant medication use during B1_P1, and any hot tub or sauna use during B1_P1. We also included established nonmodifiable risk factors (female infant sex, family history of NTDs in a first or second-degree relative, and maternal Hispanic ethnicity) to fully estimate the proportion of NTD cases attributable to all established risk factors.

Statistical Methods

Analyses were conducted separately for cases with spina bifida and anencephaly. Further, because spina bifida and anencephaly have some etiologic similarities (Lupo et al., 2010; Mitchell, 2005), analyses were also repeated among all NTD cases (i.e., cases with spina bifida or anencephaly).

Crude AFs were calculated using the following formula:

$$\text{Crude AF} = P(\text{Exposure}|\text{Disease}) * (1 - (1/\text{OR})) \quad (1)$$

where OR is the crude odds ratio for the disease-exposure association. This equation is equivalent to:

$$\text{AF} = (\text{Nobserved} - \text{Nexpected})/\text{Nobserved} = 1 - (\text{Nexpected}/\text{Nobserved}) \quad (2)$$

where Nobserved is the observed number of cases and Nexpected is the expected number of cases in the absence of exposure.

The aAFs were calculated using the method proposed by Eide and Geffler (1995), as implemented in the aflogit option of STATA (Brady, 1998). First, a multivariable logistic regression model, including all 10 risk factors, was fitted to the data. Any risk factor with an odds ratio OR) <1.00 in this model was removed because it is not meaningful to assess the proportion of risk attributable to the absence of an established risk factor. The resulting model, including only variables with OR _1.00, is referred to as the final model. Next, the aAF for the combination of all risk factors in the model was determined by recoding the values of all factors to zero (i.e., ‘‘removing’’ all exposures) and predicting the probability of disease for each individual with the new values using the final logistic regression model. The sum of these predicted probabilities provides an estimate of the number of cases that would be expected in the absence of all exposures, which was used in Equation 2 to estimate the aAF for the full combination of risk factors. The aAFs were then calculated for each variable. Briefly, variables were sequentially removed (i.e., re-coded to zero) from the final model and individual AF estimates were calculated as the difference between each subsequent reduced model and the previous model. These estimates were calculated using a generalization of Equation 1, which allows for multiple exposure strata. This process was

repeated for all possible orders of variable removal and, for each variable, AF estimates from all models were averaged to provide an estimate of its aAF.

The main analyses were repeated using data only from subjects delivered in 1999 through 2007, who would have fully benefited from folic acid fortification of the food supply. Analyses were conducted using SAS (version 9.2 copyright 2002_2008, SAS, Cary, NC) and STATA version 10 (StatCorp, College Station, TX).

RESULTS

During the study period, there were 1239 cases with an NTD and no additional, nonsecondary malformations (spina bifida N 5 836, 67.5%; anencephaly N 5 403, 32.5%) and 8494 controls. The distribution of risk factors among cases is presented in Table 1, and the crude AF for each of these factors is presented in Table 2. In the initial regression models, maternal pregestational diabetes, gestational diabetes, and hot tub or sauna use had ORs <1.00, each of which were nonsignificant for spina bifida and were excluded from the final models used in the analyses of spina bifida and all NTDs. Similarly, gestational diabetes had an OR <1.00 for anencephaly (also nonsignificant) and was excluded from the final model for this condition. The aAFs for the full combination of exposures in the final models were 27.6% for spina bifida, 44.4% for anencephaly, and 31.1% for all NTD cases.

The aAF for each exposure was also estimated (Table 2). For spina bifida, the exposures with the greatest aAFs were: maternal Hispanic ethnicity (aAF, 8.1%), obesity (aAF, 9.9%), and low dietary folate intake (4.2%). Each of the other exposures was individually responsible for an aAF <2%. For anencephaly, the exposures with the greatest aAFs were: maternal Hispanic ethnicity (aAF, 15.2%), low dietary folate intake (10.0%), female infant sex (8.7%), and lack of folic acid supplementation (4.5%). Each of the other exposures was individually responsible for an aAF <3%. When analyses were repeated for all NTD cases (i.e., cases with spina bifida or anencephaly), the aAFs were intermediate to the estimates for spina bifida and anencephaly.

As mandatory folic acid fortification of the U.S. food supply was implemented in 1998, it is possible that the risk profile of NTDs has changed over time. Consequently, because some of the subjects in this study would not have fully benefited from mandatory folic acid fortification, analyses were repeated for subjects delivered in 1999 through 2007. Results in this subgroup were similar to the main results (data not shown).

As expected, the crude AFs overestimated the combined AF as compared to the aAFs (spina bifida, 37.4% vs. 27.6%; anencephaly, 46.8% vs. 44.4%, respectively). Further, for most of the individual risk factors, the crude AF was higher than the aAF (e.g., for spina bifida, crude and adjusted AFs for Hispanic ethnicity were 11.8 and 8.1, respectively).

DISCUSSION

This study highlights the use of methods that estimate aAF, which have been underutilized in birth defects research. As expected, crude estimates of AF seemed to be inflated compared to estimates of aAF. We found that, in combination, known NTD risk factors

account for approximately 28% of spina bifida risk and 44% of anencephaly risk. Effects were generally consistent with previous estimates reported from NBDPS studies (Waller et al., 2007; Correa et al., 2008; Canfield et al., 2009; Mosley et al., 2009; Lupo et al., 2010; Duong et al., 2011; Werler et al., 2011), and any minor differences are likely because of differences in the covariates included in models or the addition of more subjects.

Attributable risks are strongly influenced by both the magnitude of association as well as the prevalence of the exposure in the population. In this study, the factors responsible for the greatest proportion of cases were common: maternal Hispanic ethnicity, obesity, low dietary folate intake, female infant sex, and lack of folic acid supplementation. By definition, eliminating risk because of exposures associated with the highest aAFs will have the greatest effect in reducing the population prevalence of NTDs. Hence, NTD prevention efforts should focus on reducing obesity rates among reproductive age women and increasing dietary folic acid intake and folic acid supplementation. Furthermore, efforts to better understand the mechanisms involved in risk due to these exposures, as well as maternal Hispanic ethnicity and female infant sex, are worthwhile, as they may lead to the identification of novel modifiable risk factors. For example, understanding why offspring of Hispanic mothers have increased risk for NTDs could help to identify underlying risk factors that could be eliminated (e.g., dietary factors). Our results suggest that eliminating the risk related to these five risk factors (maternal Hispanic ethnicity, obesity, low dietary folate intake, female infant sex, and lack of folic acid supplementation) would reduce the prevalence of NTDs by approximately 30%.

Our results indicate that, in combination, known risk factors for NTDs account for a minority of cases, as nearly 70% of disease is due to factors that remain unaccounted for. Based on the high heritability of NTDs and the high recurrence risk to siblings of affected individuals relative to the general population (Jorde et al., 1983), it is likely that a substantial proportion of NTDs are attributable to genetic factors. However, to date, no major NTD genes have been established in humans. To further elucidate the proportion of disease that cannot be accounted for by known risk factors, efforts to identify novel genetic risk factors will be critical. Such efforts should include large studies using hypothesis-generating approaches, such as genome-wide association studies and high-throughput sequencing. To account for the remaining proportion of NTD risk, novel approaches, methods, and paradigms should be developed and used to identify new nongenetic risk factors and gene-environment interactions, including novel hypothesis-generating approaches such as ‘‘environment-wide association studies’’ (Patel et al., 2010), better exposure assessment methods to reduce information bias (e.g., the use of biomarkers), and improving study designs to reduce bias and confounding (e.g., considering more homogeneous case definitions, such as clinical subtypes).

There were limitations to these analyses. The sample size for anencephaly was relatively small (N=403 cases), leading to imprecise estimates of ORs for some variables. Further, because our findings reflect the risk profile of NTDs in a population with mandatory folic acid fortification of the food supply, they may have limited generalizability to populations that have not mandated such fortification. The strengths of these analyses include use of a large, population-based dataset; separate and combined evaluation of spina bifida and

anencephaly; and adjustment of AFs. In summary, this study provides a thorough examination of the proportion of NTDs attributable to recognized risk factors. Our findings may help to identify research priorities that would maximize population-level efforts for NTD prevention.

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REFERENCES

Agopian AJ, Lupo PJ, Tinker SC, et al. Working towards a risk prediction model for neural tube defects. Birth Defects Res A Clin Mol Teratol. 2012; 94:141–146. [PubMed: 22253139]

Brady, AR. [Accessed October 27, 2012] Adjusted population attributable fractions using logistic regression. Stata Technical Bulletin. 1998. Available at: http://econpapers.repec.org/article/tsjstbull/y_3a1998_3av_3a7_3ai_3a42_3asbe21.htm.

Canfield MA, Ramadhani TA, Shaw GM, et al. Anencephaly and spina bifida among Hispanics: maternal, sociodemographic, and acculturation factors in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol. 2009; 85:637–646. [PubMed: 19334286]

Correa A, Gilboa SM, Besser LM, et al. Diabetes mellitus and birth defects. Am J Obstet Gynecol. 2008; 199:237.e1–237.e9. [PubMed: 18674752]

Duong HT, Shahrukh Hashmi S, Ramadhani T, et al. Maternal use of hot tub and major structural birth defects. Birth Defects Res A Clin Mol Teratol. 2011; 91:836–841. [PubMed: 21648056]

Eide GE. Attributable fractions for partitioning risk and evaluating disease prevention: a practical guide. Clin Respir J. 2008; 2(Suppl 1):92–103. [PubMed: 20298357]

Eide GE, Gefeller O. Sequential and average attributable fractions as aids in the selection of preventive strategies. J Clin Epidemiol. 1995; 48:645–655. [PubMed: 7730921]

Jorde LB, Fineman RM, Martin RA. Epidemiology and genetics of neural tube defects: an application of the Utah Genealogical Data Base. Am J Phys Anthropol. 1983; 62:23–31. [PubMed: 6353932]

Lupo PJ, Symanski E, Waller DK, et al. Polytomous logistic regression as a tool for exploring heterogeneity across birth defect subtypes: an example using anencephaly and spina bifida. Birth Defects Res A Clin Mol Teratol. 2010; 88:701–705. [PubMed: 20740595]

Mitchell LE. Epidemiology of neural tube defects. Am J Med Genet C Semin Med Genet. 2005; 135C: 88–94. [PubMed: 15800877]

Mosley BS, Cleves MA, Siega_Riz AM, et al. Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States. Am J Epidemiol. 2009; 169:9–17. [PubMed: 18953063]

Patel CJ, Bhattacharya J, Butte AJ. An Environment-Wide Association Study (EWAS) on type 2 diabetes mellitus. PloS One. 2010; 5:e10746. [PubMed: 20505766]

Rasmussen SA, Olney RS, Holmes LB, et al. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol. 2003; 67:193–201. [PubMed: 12797461]

Ruckinger S, von Kries R, Toschke AM. An illustration of and programs estimating attributable fractions in large scale surveys considering multiple risk factors. BMC Med Res Methodol. 2009; 9:7. [PubMed: 19166593]

Waller DK, Shaw GM, Rasmussen SA, et al. Prepregnancy obesity as a risk factor for structural birth defects. Arch Pediatr Adolesc Med. 2007; 161:745–750. [PubMed: 17679655]

Werler MM, Ahrens KA, Bosco JL, et al. Use of antiepileptic medications in pregnancy in relation to risks of birth defects. Ann Epidemiol. 2011; 21:842–850. [PubMed: 21982488]

Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. Public Health Rep. 2001; 116(Suppl 1):32–40. [PubMed: 11889273]

Table 1

Distribution o established risk factors for neural tube defects among controls and cases with isolated spina bifida or anencephaly, National Birth Defects Prevention Study, 1997–2007

	Controls[a] (N=8,494)		Spina Bifida[a] (N=836)		Anencephaly[a] (N=403)	
Risk factor	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Infant factors:						
Sex						
Male	4,314	(50.8)	414	(50.1)	163	(45.2)
Female	4,172	(49.2)	412	(49.9)	198	(54.8)
Family history of NTDs[b]						
Yes	32	(0.4)	19	(2.3)	10	(2.5)
No	8,462	(99.6)	817	(97.7)	393	(97.5)
Maternal factors:						
Race/ethnicity						
Non-Hispanic White	4,958	(58.6)	451	(54.1)	194	(48.4)
Non-Hispanic Black	935	(11.0)	65	(7.8)	28	(7.0)
Hispanic	1,918	(22.7)	265	(31.8)	144	(35.9)
Other	653	(7.7)	53	(6.4)	35	(8.7)
BMI (kg/m^2)						
Underweight (<18.5)	438	(5.4)	28	(3.6)	24	(6.4)
Normal (18.5–24.9)	4,474	(55.1)	356	(46.0)	191	(50.8)
Overweight (25.0–29.9)	1,854	(22.8)	185	(23.9)	87	(23.1)
Obese (≥30)	1,360	(16.7)	205	(26.5)	74	(19.7)
Folic acid supplementation[c,d]						
Yes	4,293	(50.7)	409	(49.1)	208	(51.6)
No	4,167	(49.3)	424	(50.9)	195	(48.4)
Low dietary folate intake (daily µg)						
Quartile 4 (>720.5)	2,107	(25.0)	193	(23.3)	92	(22.9)
Quartile 3 (496.0–720.5)	2,106	(25.0)	201	(24.3)	75	(18.7)

	Controls[a] (N=8,494)		Spina Bifida[a] (N=836)		Anencephaly[a] (N=403)	
Risk factor	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Quartile 2 (333.7–495.9)	2,107	(25.0)	202	(24.4)	103	(25.6)
Quartile 1(≤333.6)	2,107	(25.0)	232	(28.0)	132	(32.8)
Anticonvulsant use[d]						
Yes	65	(0.8)	16	(1.9)	6	(1.5)
No	8,369	(99.2)	816	(98.1)	393	(98.5)
Diabetes before index pregnancy						
Yes	51	(0.6)	3	(0.4)	8	(2.0)
No	8,423	(99.4)	831	(99.6)	395	(98.0)
Gestational diabetes during index pregnancy						
Yes	343	(4.0)	43	(5.2)	13	(3.2)
No	8,131	(96.0)	791	(94.8)	390	(96.8)
Hot tub or sauna use[d]						
Yes	488	(5.9)	40	(4.9)	24	(6.1)
No	7,852	(94.1)	780	(95.1)	370	(93.9)

[a] Characteristic totals may not equal case group totals due to missing data

[b] In first or second-degree relative

[c] Any use of folic acid, multivitamin, or prenatal vitamin supplementation

[d] During the month before pregnancy and the first month of pregnancy (B1-P1)

NTDs, neural tube defects; BMI, body mass index.

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Table 2

Adjusted attributable risk estimates for established neural tube defect risk factors among cases with isolated neural tube defects, National Birth Defects Prevention Study, 1997–2007

Variable	Exposure rate in controls	Spina bifida (N=836)				Anencephaly (N=403)				Anencephaly + spina bifida (N=1239)			
		aOR[a]	95% CI[b]	cAR[c]	aAR[d]	aOR[a]	95% CI[b]	cAR[c]	aAR[d]	aOR[a]	95% CI[b]	cAR[c]	aAR[d]
Female infant sex	49.2%	1.02	0.88–1.20	1.41	1.10	1.26	1.00–1.57	11.18	8.68	1.09	0.96–1.24	4.38	3.27
Family history of NTDs[e]	0.4%	6.99	3.87–12.60	1.90	1.78	9.19	4.38–19.31	2.11	2.18	7.45	4.41–12.59	1.97	1.86
Hispanic ethnicity	22.7%	1.54	1.29–1.84	11.78	8.05	2.19	1.71–2.82	17.13	15.15	1.71	1.48	13.52	9.86
Obesity	16.7%	1.79	1.51–2.13	11.71	9.89	1.18	0.89–1.57	3.53	2.24	1.59	1.37–1.85	9.04	7.14
No folic acid supplementation[f,g]	50.7%	1.05	0.90–1.22	3.24	1.79	1.13	0.89–1.42	--	4.51	1.07	0.94–1.22	1.65	2.57
Low dietary folate intake[h]	25%	1.22	1.03–1.44	4.02	4/15	1.61	1.26–2.04	10.44	10.04	1.32	1.14–1.52	6.12	5.66
Anticonvulsant use[f]	0.8%	2.38	1.32–4.31	1.16	0.87	2.11	0.83–5.34	0.74	0.62	2.25	1.33–3.81	1.02	0.75
Pregestational diabetes	0.6%	--	--	--	--	1.78	0.68–4.69	1.39	0.43	--	--	0.29	--
Gestational diabetes	4.1%	--	--	1.15	--	--	--	--	--	--	--	0.50	--
Hot tub or sauna use[f]	6.9%	--	--	1.02	--	1.10	0.68–1.78	0.25	0.42	--	--	0.61	--
Combined[i]				37.39	27.63			46.77	44.42			39.07	31.13

[a] Adjusted odds ratio (aOR; variables with aORs <1.00 were removed from the regression model; crude attributable risks (cARs) are not presented for variables with crude odds ratios <1.00).

[b] Confidence interval (CI).

[c] Crude attributable risk (cAR; %).

[d] Adjusted attributable risk (%).

[e] In first or second-degree relative.

[f] During the month before pregnancy and the first month of pregnancy (B1_P1).

[g] Any use of folic acid, multivitamin, or prenatal vitamin supplementation.

[h] Based on the lowest quartile of dietary folate equivalent level in controls.

[i] For crude attributable risks, the sum of individual crude attributable risks are presented.

NTDs, neural tube defects.