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The impact of folic acid intake on the association between diabetes, obesity, and spina bifida

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Abstract

Objective—To investigate the relationship between spina bifida and two established risk factors, pregestational diabetes and obesity, in both the presence and absence of the recommended daily folic acid intake in the periconceptional period.

Study Design—Cases of spina bifida (n=1154) and controls (n=9439) from the Slone Epidemiology Center Birth Defects Study (1976–2011) were included. Information on preexisting diabetes (collected 1976+) and obesity (collected 1993+), defined as BMI ≥30 kg/m^2, were collected through interviews conducted within six months of delivery. Periconceptional folic acid intake was calculated using both dietary and supplement information. Mothers were classified as consuming more or less than 400μg/day of folic acid, with food folate included at a 30% discount for its lower bioavailability. Logistic regression models, adjusted for maternal race, education, and study site, were used to calculate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the joint effects of low folic acid intake coupled with diabetes or obesity.

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Results—Mothers of cases were more likely to have diabetes or be obese (0.7% and 19.0%, respectively) than control mothers (0.4% and 10.8%, respectively). The joint effect of diabetes and lower folic acid intake on spina bifida was larger (aOR:3.95; CI: 1.56, 10.00) than that of diabetes and higher folic acid intake (aOR:1.31; CI: 0.17, 10.30). Folic acid intake made little difference on the association between obesity and spina bifida.

Conclusion—Our findings suggest that folic acid further attenuates, though does not eliminate, the risk of spina bifida associated with diabetes, than that with obesity.

Keywords

folic acid; obesity; preexisting diabetes; pregnancy; spina bifida

Introduction

Folic acid intake in the periconceptional period reduces the risk of spina bifida in offspring[1–4]. Spina bifida, a neural tube defect, develops in the earliest part of pregnancy, frequently prior to recognition of pregnancy. Due to this early developmental timing and the fact that approximately half of all pregnancies in the United States are unplanned[5], the United States Public Health Service, the Institute of Medicine[6], and the United States Preventive Services Task Force[7] recommend that women of child-bearing age consume at least 400μg of folic acid daily through supplements and fortified food products[8]. Despite these recommendations and mandatory fortification of enriched cereal grain products beginning in the U.S. in 1998, a recent study estimated that only one in four women of child-bearing age consumes the recommended amount of folic acid[9]. Given the established role of folic acid in reducing the occurrence of spina bifida, it is possible that risk factors for spina bifida may operate differently in the presence and absence of folic acid.

Preexisting diabetes and obesity have both been identified as independent risk factors for spina bifida[10–13], yet few studies have addressed the impact of folic acid intake on these associations. In animal studies, folic acid supplementation has been shown to decrease the incidence of neural tube defects among diabetic pregnancies[14,15]. The only epidemiologic study conducted to date observed that diabetic women using folic acid-containing supplements had a lower risk of spina bifida than non-supplementing diabetic women[16]. Similarities in the physiology of diabetes and obesity, including abnormalities in glucose metabolism, might suggest that folic acid may also affect the association between obesity and spina bifida. A studyof prepregnancy weight and neural tube defects observed that folic acid offered some protection among lighter women (<70 kg), but no such protection among heavier women[17].

With recent studies suggesting that, in the era of folic acid fortification, achieving higher levels of folic acid intake through supplement use[18,19] and dietary folate[19] may not reduce the risk of neural tube defects, it is important to understand if higher levels of folic acid intake alter the effect of other risk factors for spina bifida. Using data from the Slone Epidemiology Center Birth Defects Study, we sought to describe the effect of obesity and diabetes on the risk of spina bifida in both the presence and absence of the recommended amount of daily folic acid intake.

Materials and Methods

Study Population

The Slone Epidemiology Center Birth Defects Study is an on-going case-control study in the United States and Canada that began in 1976. Cases of birth defects are ascertained from birth hospitals, tertiary care centers, or birth defects registries in Massachusetts(1976+); Philadelphia, PA(1976+); San Diego, CA(2001+); Toronto, Canada(1976–2005); selected counties in Iowa(1983–1985); and parts of New York State(2004+). Cases include livebirths, fetal deaths(1990+), and elective terminations(1990+). Controls are liveborn infants selected from study hospitals and birth certificates of the catchment area from which cases were collected. Prior to 1993, controls consisted of infants with minor malformations, such as heart murmurs and skin tags. Beginning in 1993, non-malformed infants were used. The study has been approved by the Boston University Institutional Review Board and is in compliance with the Health Insurance Portability and Accountability Act.

A maternal interview is conducted by a trained nurse within six months of delivery among subjects providing informed consent. The interview includes questions on reproductive history, medication use and illnesses during pregnancy. Beginning in 1988, data on diet were collected using a food frequency questionnaire (FFQ).

The present study includes cases of spina bifida and controls ascertained between 1976 through 2011. Spina bifida cases were excluded in the presence of chromosomal anomalies, Mendelian inherited disorders, recognized syndromes, amniotic bands, body wall defects, or conjoined twins. Cases were reviewed by a clinical geneticist and classified into isolated and multiple defect categories. Cases were considered multiple if another major defect, unrelated to spina bifida, was present.

Diabetes and Obesity

Information on diabetes, both preexisting and gestational, was collected throughout all years of the study. Preexisting diabetes was defined as the onset of type 1 or type 2 diabetes prior to pregnancy. Gestational diabetes was defined as the onset of diabetes after the first lunar month of the index pregnancy. Body mass index (BMI) was calculated based on the mother's self-reported height and prepregnancy weight. Data on BMI were available from 1993 onwards when information on maternal height was incorporated into the interview. BMI was categorized into four groups; underweight (<18.5 kg/m^2), normal-weight (18.5–24.9 kg/m^2), overweight (25– 29.9 kg/m^2), and obese (≥30 kg/m^2)[20].

Folic Acid Intake Assessment

Folic acid intake in the periconceptional period, defined as the month prior to the last menstrual period through the first lunar month of pregnancy, was calculated by summing average daily folic acid intake from supplements and fortified foods. Natural folate from diet was also included, but discounted by 30% due to its lower bioavailability[6]. Data on dietary intake was collected from an adapted Willett FFQ. The FFQ asked about diet in the six months prior to pregnancy to best capture nutritional intake in the periconceptional period. Dietary values of folic acid and folate were adjusted for total energy intake using the

residual method[21]. Subjects were categorized into two groups, those achieving the recommended intake of ≥400μg /day of folic acid (high intake) and those with an intake of <400 μg/day (low intake). Subjects with extreme caloric intake (<500 or >4,000 kcal/day) and incomplete (≥3 missing items) FFQs were excluded from analyses involving folic acid intake; however, two exceptions were made. Women reporting ≥400μg of daily folic acid from vitamin supplementation remained in the analysis, because regardless of dietary intake they would be included in the ≥400μg/day category. Secondly, women reporting no supplementation remained in the analysis because regardless of dietary intake it is unlikely they would reach ≥400μg/day of folic acid[9]. Women with missing information on diet and an intake of <400μg/day from supplementation were excluded.

Statistical Analyses

Logistic regression models were used to calculate odds ratios and 95% confidence intervals (95%CI). We calculated crude and adjusted odds ratios (cOR and aOR, respectively) for the associations between spina bifida and preexisting diabetes and gestational diabetes, separately. To assess the joint effect of low folic acid intake on the association between preexisting diabetes and spina bifida, subjects were categorized into four unique groups; (1) no diabetes and ≥400μg/day folic acid (referent), (2) diabetes and ≥400μg/day of folic acid, (3) no diabetes and <400μg/day of folic acid, and (4) diabetes and <400μg/day of folic acid. The relative excess risk due to interaction (RERI) and 95% CI between diabetes and low folic acid intake was calculated. Women with gestational diabetes were excluded from the analysis of joint effect.

Analyses in which BMI was assessed were restricted to 1993–2011 birth years and excluded women with preexisting diabetes. We calculated odds ratios for underweight, overweight, and obese groups. To assess the joint effect of low folic acid intake and obesity, subjects were categorized into four unique groups; (1) normal-weight and ≥400μg/day of folic acid (referent), (2) obese and ≥400μg/day of folic acid, (3) normal-weight and <400μg/day of folic acid, and (4) obese and <400μg/day of folic acid. The RERI and 95% CI was calculated. BMI data were missing for 2.5% percent of participants and missing BMI did not appear to be independent of other analytic variables. Therefore, we conducted a sensitivity analysis in which multiple imputation methods were used to impute BMI; the impact of using these imputed values to estimate the association between BMI and spina bifida was assessed. Due to changes in case and control ascertainment over the study period, a sensitivity analysis to address the possibility of selection bias was performed by restricting cases and controls to those from the same birth hospitals. Maternal age, education, race, study site, and folic acid intake (<400μg/day, ≥400μg/day) were included in regression models to adjust for potential confounding. Joint effect models did not include folic acid intake as a covariate. Analyses were performed using SAS software 9.3.

Results

Diabetes

A total of 1,154 cases of spina bifida and 9,439 controls ascertained between 1976 through 2011 were included in the diabetes analysis. Cases and controls differed byrace/ethnicity,

maternal age, education, and folic acid intake (Table 1). Among case mothers, the prevalence of preexisting diabetes was 0.69% compared to 0.44% among control mothers. The aOR for preexisting diabetes and spina bifida was 1.84 (95% CI:0.80, 4.22); that for gestational diabetes was 1.19 (95% CI:0.84, 1.71)(Table 2). Spina bifida in the presence of other defects had an aOR of 2.56 (95% CI:0.59, 11.13) for preexisting diabetes, while that for isolated spina bifida was 1.70 (95% CI:0.68, 4.29)(data not shown).

The joint effect of low folic acid intake and preexisting diabetes resulted in 4-fold increased risk for spina bifida (aOR:3.95, 95%CI:1.56,10.00) relative to mothers without diabetes and with higher daily folic acid intake, which was greater than expected given the individual additive effects of low folic acid intake and preexisting diabetes (RERI:1.65, 95% CI: 2.87,6.18). In the presence of ≥400μg/day of folic acid, this association was attenuated (aOR:1.31, 95% CI: 0.17, 10.30), although this estimate was based on one exposed case (Table 3).

Sensitivity analyses restricted to cases and controls from the same birth hospitals changed diabetes results modestly, but the RERI still indicated synergy between diabetes and low folic acid intake (data not shown).

Obesity

Restrictions to the years in which data on BMI were available and exclusion of women with preexisting diabetes yielded a total of 389 cases and 8062 controls in the BMI analysis. During this time period, cases and controls differed by maternal age, education and folic acid intake (Table 1). Among case mothers, 19.0% were obese compared to 10.8% of control mothers. The aOR for spina bifida among overweight women was 1.24 (95% CI: 0.93, 1.63); that for obese women was 1.97 (95% CI:1.46, 2.65) (Table 4). Overall, 4.37% of cases and 2.44% of controls were missing data on BMI, with Hispanic mothers more likely to have missing BMI data (15.8% of cases and 9.4% of controls) (data not shown). Multiple imputation of BMI did not materially change the results (Table 4).

There did not appear to be a joint effect between obesity and folic acid intake (RERI: 0.14, 95% CI: 1.08, 1.35). With normal-weight and higher folic acid intake as the referent, the aOR for obesity and low folic acid intake was 2.43 (95%CI: 1.63, 3.63), which is expected under the assumption of independent additive associations of obesity and low folic acid intake (Table 5).

Obesity results remained unchanged when restricted to cases and controls from the same birth hospitals (data not shown).

Comment

Failure to achieve the recommended intake of folic acid during the periconceptional period is suggestive of a further increase in the risk for spina bifida among mothers with preexisting diabetes, while the increased risk among obese mothers was not more than expected.

We observed a two-fold increased risk of spina bifida among women with preexisting diabetes, but the estimate was unstable due to a small number of diabetic cases. Although

other studies to date have considered the relationship between preexisting diabetes and the combined group of all neural tube defects, including spina bifida and anencephaly, few have quantified the association between diabetes and spina bifida, specifically. Our odds ratio, based on eight exposed cases, was well above the estimates observed in two previous studies, which reported odds ratios of 0.4 (0–4.4) and 0.75 (0.17–3.24)[22,23], but was smaller in magnitude than that reported from a cohort study in Nova Scotia (RR: 17.2, 2.3–128.8)[24]. Findings were similar to those from a study with an odds ratio of 1.81 (0.53–6.20) for non-Hispanic whites[25]. Of note, the previous findings were each based on less than four exposed cases.

Our observation regarding the joint effect of folic acid intake and diabetes are consistent with that previously reported[16]. In the study by Correa et al., the odds ratio for spina bifida among mothers who used folic acid-containing supplements and had preexisting diabetes was 1.66(0.62–4.42), compatible with the 1.31(0.17–10.30) we observed. Our risk estimate for diabetic mothers who did not consume the recommended intake of folic acid was somewhat larger than the odds ratio reported for the equivalent group in that study (i.e., diabetics not using supplements), 3.95 and 2.37, respectively[16]. It should be noted that the previous study did not include dietary intake of folic acid and defined the window of folic acid intake as the month prior to conception through the first three months of pregnancy; in contrast, the present study included dietary intake of both synthetic folic acid and natural food folate and estimated daily folic acid intake during the month before and after the last menstrual period. The neural tube closes during the second month of pregnancy and the proportion of women taking supplements vastly increases during the second and third month, which would contribute to misclassification of folic acid intake.

The mechanism by which folic acid may reduce the risk of spina bifida due to diabetic embryopathy is not well understood. It has been proposed that folic acid has antioxidant properties that mitigate the effect of reactive oxygen species and abnormal apoptosis resulting from diabetes[15,26,27]. A potential explanation of our findings involves the ability of folic acid to reduce oxidative stress in the embryo caused by increased levels of glucose. Oxidative stress leads to reduced expression of the Pax3 gene which may result in malformation of the neural tube[27]. In addition to folic acid, other antioxidants have been shown to reduce the occurrence of malformations in diabetic animal models[28,29].

Few studies have addressed the association between diabetes and spina bifida specifically, and those displayed inconsistent results; on the other hand, research on obesity and spina bifida is more abundant and results more consistent. Data from the present investigation are consistent with previously published studies reporting odds ratios ranging from 1.5 to 3.5[10,12] contributing to the growing body of evidence supporting a two-fold increase in the risk of spina bifida among obese women.

The risk of spina bifida among obese women achieving the recommended intake of folic acid was comparable with the risk among obese women who did not consume the recommended amount. This finding is consistent with a previous study, based on the same data source in a different time period as the present study, that observed that 400μg/day of folic acid was not protective against neural tube defects among heavier women, defined as

>70 kg[17]. In a study comparing risks of neural tube defects by maternal weight categories in pre-fortification and post-fortification time periods, the reduction in risk was lowest among women in the highest weight quartile[30]. Serum folate levels have been shown to be lower among obese women, even after controlling for folic acid intake[31]. It has been estimated that obese women need to consume an additional 350μg/day of folic acid to achieve the same serum levels of folate as women in the lowest BMI category[31].

Strengths of this study are the large sample size and the amount of diabetic cases, more than in previous studies. Another strength of this study is the short interval between delivery and interview. The short time period between delivery and interview likely improved the mothers' reporting accuracy. Lastly, we were able to include both diet and supplements in the calculation of folic acid intake. The FFQ asked about diet in the six months prior to the last menstrual period, which is likely reflective of diet in early pregnancy and neural tube development. Furthermore, dietary data were available from a validated FFQ and the Slone Birth Defect Study has a comprehensive database of supplement information which improved classification of folic acid in specific supplement products over time.

Despite these strengths, some limitations should be considered when interpreting the results. Data on preexisting diabetes and obesity were collected by maternal report, which may have resulted in misclassification. The prevalence of previously diagnosed diabetes among women aged 20–39, from 1988–1994, was 1.1%[32]. The reported prevalence of preexisting diabetes among control mothers in our study was 0.44%. The estimated prevalence of prepregnancy obesity in the U.S. from 1993 to 2003 ranges from 13–22%[33]. In the present study, the prevalence among controls was 11%. In addition to underreporting, time trends and demographic differences may explain some of the discrepancy between published prevalences of diabetes and obesity and those reported in our study. Observed associations would have been attenuated if misclassification of preexisting diabetes and obesity was similar for cases and controls.

A limitation that may have affected our findings regarding diabetes, folic acid, and spina bifida is lack of information of glycemic control. Enhanced glycemic control during pregnancy reduces the rate of birth defects to levels similar to the general population[34–36]. Additionally, diabetic women who achieve glycemic control are more likely to have preconception care and subsequently more likely to take folic acid supplements[37]. We could not determine if the observed reduction in risk was due to higher folic acid intake or to glycemic control. Another limitation of the diabetes analysis was lack of data on BMI prior to 1993, making it infeasible to include BMI in the multivariate analyses for all study years. However, pre-pregnancy weight was available for all years of the study, and a sub-analysis adjusting for pre-pregnancy weight yielded comparable results (data not shown). Additionally, we lacked dietary data prior to 1988. However, it is expected that the contribution of diet to overall folic acid intake would be low prior to fortification.

In summary, achieving the daily recommended intake of ≥400μg of folic acid reduced the risk of spina bifida, yet this level of intake had a greater effect on reducing the risk of spina bifida due to diabetes than that due to obesity. An understanding of the mechanism by which diabetes appears to increase the risk for spina bifida and how folic acid may reduce its

teratogenicity would provide more insight into whether or not higher levels of folic acid intake has the potential to further attenuate the risk of spina bifida due to obesity.

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Table 1

Maternal Characteristics of Spina Bifida Cases and Controls, Slone Birth Defects Study

	1976–2011[a]				1993–2011[b]			
	Spina Bifida Cases		Controls[c]		Spina Bifida Cases		Controls	
	No.	%	No.	%	No.	%	No.	%
Total	1154		9439		389		8062	
Maternal race/ethnicity								
White, non-Hispanic	991	85.9%	7112	75.3%	279	71.7%	5816	72.1%
Black, non-Hispanic	58	5.0%	628	6.7%	30	7.7%	580	7.2%
Other races	105	9.1%	1693	17.9%	80	20.6%	1660	20.6%
Hispanic[d]	73	6.3%	1095	11.6%	57	14.7%	1079	13.4%
Missing data	0	0.0%	6	0.1%	0	0.0%	6	0.1%
Maternal age at conception								
<20 years	92	8.0%	594	6.3%	24	6.2%	535	6.6%
20–24 years	263	22.8%	1441	15.3%	57	14.7%	1122	13.9%
25–29 years	390	33.8%	2687	28.5%	136	35.0%	2143	26.6%
30–34 years	296	25.6%	3125	33.1%	109	28.0%	2767	34.3%
35–39 years	94	8.1%	1371	14.5%	53	13.6%	1287	16.0%
≥40 years	19	1.6%	200	2.1%	10	2.6%	188	2.3%
Missing data	0	0.0%	21	0.2%	0	0.0%	20	0.2%
Maternal education								
<12years	178	15.4%	854	9.0%	63	16.2%	701	8.7%
12 years	418	36.2%	1964	20.8%	104	26.7%	1479	18.3%
>12 years	557	48.3%	6614	70.1%	222	57.1%	5877	72.9%
Missing data	1	0.1%	7	0.1%	0	0.0%	5	0.1%
Study center (years in study)								
Boston (1976+)	300	26.0%	4491	47.6%	84	21.6%	4121	51.1%
Philadelphia (1976+)	417	36.1%	2173	23.0%	137	35.2%	1581	19.6%
Toronto (1979–2005)	359	31.1%	1236	13.1%	106	27.2%	960	11.9%

	1976–2011[a]				1993–2011[b]			
	Spina Bifida Cases		Controls[c]		Spina Bifida Cases		Controls	
	No.	%	No.	%	No.	%	No.	%
Iowa (1983–1985)	15	1.3%	132	1.4%	--	--	--	--
San Diego (2001+)	33	2.9%	1007	10.7%	32	8.2%	1002	12.4%
New York (2004+)	30	2.6%	400	4.2%	30	7.7%	398	4.9%
Daily folic acid intake								
<400 μg	832	72.1%	5023	53.2%	225	57.8%	4005	49.7%
≥400 μg	259	22.4%	3991	42.3%	139	35.7%	3797	47.1%
Missing data	63	5.5%	425	4.5%	25	6.4%	260	3.2%

[a] Diabetes analysis

[b] Obesity analysis

[c] From 1976–1993 cases with minor malformations were used as controls

[d] Hispanic ethnicity was ascertained from 1983 onwards

Table 2

Crude and Adjusted Odds Ratios and 95% Confidence Intervals for the Association between Diabetes and Spina Bifida, Slone Birth Defects Study, 1976–2011

	Cases (n=1154)		Controls (n=9439)		cOR (95% CI)	aOR[a] (95% CI)
Diabetes	n	%	n	%		
Pre-existing	8	0.69%	42	0.44%	1.56 (0.73, 3.32)	1.84 (0.80, 4.22)
Gestational	39	3.38%	371	3.93%	0.86 (0.61, 1.20)	1.19 (0.84, 1.71)
None	1107	95.93%	9026	95.62%	1.0 (ref)	1.0 (ref)

aOR: adjusted odds ratio; CI: confidence interval; cOR: crude odds ratio

[a]Adjusted for maternal age, education, race/ethnicity, folic acid intake, and study center

Table 3

The Joint Effect of Folic Acid Intake and Diabetes and the Risk of Spina Bifida, Slone Birth Defects Study, 1976–2011

Preexisting Diabetes	<400 μg Folic Acid	Ca/Co	aOR[a] (95% CI)
No	No	242/3827	1.0 (ref)
No	Yes	803/4798	1.99 (1.69, 2.34)
Yes	No	1/15	1.31 (0.17, 10.30)
Yes	Yes	7/24	3.95 (1.56, 10.00)
RERI (95% CI): 1.65 (−2.87, 6.18)			

aOR: adjusted odds ratio; CI: confidence interval; RERI: relative excess risk due to interaction

[a]Adjusted for maternal age, education, race/ethnicity, and study center

Table 4

Crude, Adjusted, and Imputed Odds Ratios and 95% Confidence Intervals for the Association between Body Mass Index and Spina Bifida, Slone Birth Defects Study, 1993–2011

	Cases (n=389)		Controls (n=8062)		Observed Data cOR (95% CI)	Observed Data aOR[a] (95% CI)	Imputed Data aOR[a] (95% CI)
	n	%	n	%			
Body Mass Index (kg/m^2)							
Underweight (<18.5)	20	5.14%	476	5.90%	1.07 (0.67, 1.70)	1.00 (0.62, 1.62)	0.99 (0.60,1.61)
Normal (18.5 – 24.9)	197	50.64%	4992	61.92%	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight (25 – 29.9)	81	20.82%	1529	18.97%	1.34 (1.03, 1.75)	1.24 (0.93, 1.63)	1.22 (0.93, 1.62)
Obese (≥ 30)	74	19.02%	868	10.77%	2.16 (1.64, 2.85)	1.97 (1.46, 2.65)	1.97 (1.47, 2.65)
Missing	17	4.37%	197	2.44%	---	---	---

aOR: adjusted odds ratio; CI: confidence interval; cOR: crude odds ratio

[a]Adjusted for maternal age, education, race/ethnicity, folic acid intake, and study center

Table 5

The Joint Effect of Folic Acid Intake and Obesity and the Risk of Spina Bifida, Slone Birth Defects Study, 1993–2011

Obese	< 400 μg Folic Acid	Ca/Co	aOR[a] (95% CI)
No	No	80/2494	1.0 (ref)
No	Yes	102/2333	1.22 (0.89, 1.68)
Yes	No	23/340	2.08 (1.27, 3.39)
Yes	Yes	48/506	2.43 (1.63, 3.63)
RERI (95% CI): 0.14 (−1.08, 1.35)			

aOR: adjusted odds ratio; CI: confidence interval; RERI: relative excess risk due to interaction

[a]Adjusted for maternal age, education, race/ethnicity, and study center