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Maternal dietary glycemc intake during pregnancy and the risk of birth defects

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Summary

High sugar intake has been linked to fetal anomalies in the presence and absence of insulin resistance. Using dietary data collected in the Boston University Slone Epidemiology Birth Defects Study, we examined whether high dietary glycemc index (dGI) or load (dGL) increased the risk of birth defects. Non-diabetic mothers of 1,921 cases and 704 controls were interviewed within six months after delivery (1988–1998) about pregnancy events and exposures, including a 99-item food frequency questionnaire. Case groups included amniotic bands, craniosynostosis, gastroschisis, hypospadias, small intestinal defects, anorectal defects, limb reductions, omphalocele, cleft lip and/or palate, renal agenesis, and tracheoesophageal fistula. Cubic splines were used to determine cutpoints values for high dGI and dGL in relation to the risk of each birth defect. The cutpoints were used in logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI). Control mothers in the lowest quartile of glycemc intake were more likely to be non-Hispanic White, 30 years of age, have higher family income, have a normal body mass index, and reside in Boston. Findings were null for most case groups. The anorectal defect case group was found to have elevated risks for dGL [adjusted OR: 2.35; 95% CI: 1.1, 4.9], while estimates for dGI were elevated for the amniotic band case group [adjusted OR: 3.01; 95% CI: 1.1, 8.1]. Because this is the first paper (to our knowledge) to explore dGI and dGL in relation to a spectrum of birth defects, additional studies are needed.

Background

The importance of maternal diet in fetal development is well established^{1, 2} and indeed certain nutrients have been linked to birth defects in both animals and humans.^{3–6} As one such example, high sugar intake has been linked to fetal anomalies in the presence and absence of insulin resistance.^{7–12} Maternal dietary glycemc intake measures both the carbohydrate content of specific food and the actual blood glucose response to that particular food.^{13, 14} Diets with high glycemc levels have been associated with neural tube defects in two studies,^{11, 12} but have not been studied in relation to risks of other specific birth defects. To address this research question, the present analysis utilized food frequency data collected retrospectively for the time period immediately preceding pregnancy on 2,625 mothers whose pregnancies were or were not affected with birth defects.

Methods

The Slone Birth Defects Study (also called the Pregnancy Health Interview Study) is an ongoing multi-center case-control study that was initiated in 1976 as a surveillance program to identify risk factors for birth defects; it has been previously described in detail.^{3, 15} The present analysis focuses on data collected from 1988 through 1998, when dietary intake was assessed with a 99-item Willett Food Frequency Questionnaire (FFQ). Cases were identified from birth hospitals and tertiary care hospitals in the areas surrounding Boston, Massachusetts, Philadelphia, Pennsylvania, and Toronto, Canada. Beginning in 1990, cases from elective terminations were included in the study. In 1993, infants with no major congenital anomalies were identified as controls and ascertained from the same population as the cases.

Cases were classified into 10 malformation groups that had sufficient numbers for analysis: amniotic bands, craniosynostosis, gastroschisis, hypospadias, small intestinal defects (excluding gastroschisis and omphalocele), anorectal defects (excluding sirenomyelia and caudal regression), limb reductions (excluding amniotic bands), omphalocele, cleft lip and/or palate (excluding holoprosencephaly), renal agenesis (unilateral and bilateral), and tracheoesophageal fistula. Any case with a conjoined twin, a chromosomal anomaly, a known syndrome or incomplete diagnostic information was excluded. Cases were further classified as isolated if there were no other secondary major malformations. For amniotic bands, isolated cases excluded those with evidence of a body wall defect.

Interviews were conducted in person by trained nurses within 6 months of delivery. Mothers were asked about their demographic information, reproductive history, exposures during pregnancy including, medications and vitamin use, illness history, and diet. To assess dietary intake, the 99-item Willett FFQ was utilized. Dietary patterns were assessed for the 6 months prior to pregnancy to capture a woman's usual intake before she was aware of her pregnancy, after which she might change her eating habits. Because much of organogenesis is vulnerable early in the first trimester, and since recognition of pregnancy may occur during this time, dietary intake before pregnancy is recognized as a better indicator of exposure during the relevant time period. Data on women who had more than 3 missing responses in the FFQ were considered to be unreliable and were excluded from the analysis. In addition, women who reported extreme caloric intake (<500 kcal/day or >3800 kcal/day), eating implausible amounts of food (more than 20 separate items on a daily basis), pre-existing or gestational diabetes were excluded from the analysis.

Glycemic index is a relative measure of the blood glucose-raising potentials of carbohydrate-containing foods. To calculate dietary glycemic load (dGL), the glycemic index of each reported food was multiplied by the carbohydrate content of the food and then multiplied by the reported number of daily servings and summed up over all the foods reported in the FFQ. Dietary glycemic index (dGI) was calculated by dividing dGL by the total amount of carbohydrate consumed. As a result of removing the quantity of carbohydrate consumed, dGI better measures the quality of carbohydrate consumed in a diet, while dGL measures both the quality and quantity of carbohydrate consumed.¹⁶ Dietary values for individual foods were obtained from the Harvard University Food Composition Database derived from the US Department of Agriculture Database.¹⁷

Cubic-spline logistic models with 5 knots were created for each case group to compare glycemic intake between case and control mothers. If a diverging effect was visible in the spline, a cut-point was identified by locating where the spline crossed an odds ratio (OR) of 1.5 and that glycemic value was used for dichotomizing dGI or dGL in subsequent analyses. Crude and adjusted ORs and 95% confidence intervals (CI) were calculated for each case

group. Sociodemographic factors that were taken into consideration in the analysis included: maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other race), maternal age (<20, 20–24, 25–29, 30–34, 35), income in 2005 US dollars (<\$15,000, \$15,000–\$30,000, \$30,000–\$44,999, and \$45,000) and center (Boston, Philadelphia, and Toronto). All analysis were performed using SAS 9.1 software.¹⁸

Results

There were a total of 1,921 cases and 704 controls included in the analysis. The case groups consisted of children with amniotic bands (N=48), anorectal defects (N=160), craniosynostosis (N= 189), gastroschisis (N= 78), hypospadias (N=241), limb reduction (N= 183), omphalocele (N=115), orofacial clefts (N=626), renal agenesis (N=47), small intestinal defects (N= 79), and tracheoesophageal fistula (N=168) cases. For the purpose of describing the demographic distributions according to glycemic intake, we compared control mothers in the highest quartile to the lowest quartile of dGI and dGL intakes (Table 1). Control mothers in the lowest quartile were more likely to be non-Hispanic white, be at least 30 years of age, have higher family incomes (> \$45,000), have a normal body mass index (18.5–24.9 kg/m²), and reside in greater metropolitan Boston.

For dGI, 9 of the 11 case groups had splines that indicated an increased risk of the outcome with higher levels of intake. The cut-points identified for dGI ranged from 58 to 64 and are presented in Table 2 along with the accompanying ORs. The spline for the amniotic case group (Figure 1a) indicated an increase in risk at dGI = 62 [adjusted OR: 3.01; 95% CI: 1.1, 8.1]. Suggestions of increased risks were observed for anorectal defects [dGI = 60, adjusted OR: 1.54; 95% CI: 1.0, 2.5], craniosynostosis [dGI = 61, adjusted OR: 1.79; 95% CI: 1.0, 3.2], hypospadias [dGI = 63, crude OR: 1.89; 95% CI: 0.7, 5.1], and small intestinal defects [dGI = 62, adjusted OR: 2.04; 95% CI: 0.8, 4.9].

The splines for dGL revealed diverging effects across a broader range of values, from 192 to 230. For the anorectal defects case group, 11% of cases had dGL greater than or equal to 192 compared to 5% of controls [adjusted OR: 2.35; 95% CI: 1.1, 4.9], the spline for this case group can be seen in Figure 1b. High dGL intakes, based on spline cut-offs, were more common than controls for craniosynostosis, limb reduction defects, orofacial clefts, and tracheoesophageal fistula case groups, but OR estimates were unstable due to small numbers.

When we restricted the analysis to isolated case groups (Table 3), increases in odds ratios for both dGI and dGL were similar to those observed for the overall amniotic bands, anorectal defects, hypospadias, orofacial clefts, and small intestinal defects.

Because non-malformed controls were not collected before 1993, we restricted analysis to 1993 onwards. Findings were generally similar for this subgroup. However, ORs were stronger for amniotic bands and dGI (crude OR: 6.55; 95% CI: 2.0, 21.5) and for anorectal defects and dGL (crude OR: 4.05; 95% CI: 1.9, 8.5).

Discussion

High levels of dietary glycemic intakes were not associated with most of the malformation groups, at least within the distribution of intakes measured in this study population. Spline regressions, for the most part, did not reveal case–control divergence at higher levels. Null findings for the majority of case groups may indicate no true role for glycemic intake; on the other hand, it is also possible that divergence between some case groups and controls may exist, but at levels of glycemic intake that are higher than observed in this study population. A study of neural tube defects from this same dataset identified an approximately two-fold

increased risk associated with a dGI of 60 and dGL of 205.¹² The possibility that other birth defects might be less sensitive to hyperglycemia than NTDs, meaning divergence occurs at a higher glycemic value, would be consistent with previous findings for diabetes and obesity, which show the greatest risks for NTDs.^{19–22}

For both dGI and dGL, elevated risks were seen for anorectal defects, though the lower 95% confidence interval included 1.0 for dGI. Diabetes is a risk factor for this group of defects,^{23–28} but our odds ratio estimates for glycemic intake were independent of diabetes because women with either pre-existing or gestational diabetes were excluded. We can not rule out the possibility that undiagnosed diabetes may account for some of the effect seen. If the observed elevated odds ratios for high glycemic intake are indeed real, then hyperglycemia with or without diabetes may be involved in the developmental of the lower bowel. Obesity may also be involved, since it has been shown to increase the risk of anorectal defects.²⁰ However, there was an insufficient number of heavier women with higher levels of glycemic intake to examine this relationship in our data. Similar to previous findings for NTDs, both high dietary glycemic index and load showed increased risks of anorectal defects, suggesting both carbohydrate quality and quantity may be important risk factors. More than half of anorectal defect cases had associated defects, including some with NTDs, but odds ratios remained elevated for isolated cases (albeit with wider confidence intervals), providing additional evidence supporting an etiologic role for hyperglycemia in lower bowel development.

Cases with amniotic bands were also associated with glycemic intake, but unlike anorectal defects and NTDs, the effect appeared to be confined to carbohydrate quality (dGI). All amniotic band cases exposed to dGI ≥ 62 were considered isolated (i.e., there was no evidence of a body wall defect) and the OR was increased 4-fold for this subgroup. There have been few studies of risk factors for amniotic bands, owing to its rarity, and none have considered dietary factors or diabetes.²⁹ One study with only 12 amniotic band cases reported no association for obesity.²¹ Young maternal age³⁰ and low socioeconomic status²⁹ have been identified as risk factors for amniotic bands but the increased risks associated with high dGI are independent of age and income.

The strengths of this study are its large size and multiple centers that represent geographically distinct areas of the country. However, some case groups may be etiologically heterogeneous (e.g., small intestinal defect groups). An effort was made to collect accurate exposure histories by administering standardized questionnaires in-person within 6 months of birth. The opportunity for reporting bias is a potential limitation in case-control studies; however the short interval between interview and birth in this study likely increases the accuracy of responses from participants, regardless of case/control status, thereby reducing chances of non-differential reporting bias. In addition, differential reporting bias (so-called recall bias) is less likely because interviews were conducted at a time when little was known about carbohydrate intake as a risk factor for birth defects. A methodological strength of this study was the use of splines which allows for all the data points to be used to better understand the relationship between the exposure and outcome while not constraining the data with artificially-imposed categories.^{31–33} The focus of our study was on dGI and dGL as individual exposures; while studies have shown that individual glycemic levels are able to predict the carbohydrate content of mixed meals,^{34, 35} we can not rule out that micronutrients, antioxidant or other nutrients may be involved in the associations that were identified in this study. There is a possibility of non-differential misclassification of dietary glycemic intake which would most likely attenuate findings, and could account for the null observations for most defects. If so, the observed associations may also be underestimates of the truth. The use of the long version Willett FFQ is another strength of this study, as a previous analysis has found that it better captures glycemic intake

than the shortened questionnaire.¹² The Willett FFQ has also been validated for use in epidemiologic studies with pregnant women.³⁶ There is the possibility that dietary recall can differ by maternal attributes that are associated with birth defects; though our findings varied across different birth defects, we can not rule out the potential for recall bias.³⁷ Another limitation is that some case groups may not have had enough subjects at the higher end of the exposure distribution where an increased risk may reside. In addition, while some case groups had elevated ORs, they may have not been large enough for stable risk estimation. Despite many comparisons, we made no corrections for multiple testing because this is the first paper to our knowledge to examine dGI and dGL in relation to non-CNS anomalies thus is exploratory in nature. Additional studies are necessary to confirm or refute our findings.

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A)

B)

Figure 1.

Adjusted cubic splines for A) amniotic bands and dietary glycemic index and B) anorectal defects and glycemic load, United States and Canada, 1988–1998. The splines were adjusted for maternal race, maternal age, center, income, and (in glycemic load models only) fiber. The 95% confidence intervals are represented by the shaded area.

Table 1
Characteristic of Mothers with No Major Malformation by Glycemic Intake, United States and Canada, 1993–1998

	Dietary Glycemic Index				Dietary Glycemic Load					
	1st Quartile		4th Quartile		1st Quartile		4th Quartile			
	N	%	N	%	N	%	N	%		
Race/Ethnicity										
Non-Hispanic White	170	96.6%	147	83.5%	317	167	94.9%	149	84.7%	316
Non-Hispanic Black	1	0.6%	21	11.9%	22	5	2.8%	17	9.7%	22
Other	1	0.6%	4	2.3%	5	1	0.6%	7	4.0%	8
Hispanic	4	2.3%	4	2.3%	8	3	1.7%	3	1.7%	6
Maternal Age										
< 20	4	2.3%	10	5.7%	14	4	2.3%	7	4.0%	11
20–24	16	9.1%	22	12.5%	38	16	9.1%	21	11.9%	37
25–29	47	26.7%	67	38.1%	114	52	29.5%	63	35.8%	115
30–34	72	40.9%	61	34.7%	133	76	43.2%	66	37.5%	142
35	37	21.0%	16	9.1%	53	28	15.9%	19	10.8%	47
Center										
Boston	68	38.6%	53	30.1%	121	69	39.2%	42	23.9%	111
Phil	39	22.2%	42	23.9%	81	37	21.0%	50	28.4%	87
Toronto	69	39.2%	81	46.0%	150	70	39.8%	84	47.7%	154
Income (2005 Dollars)										
Missing	6	3.4%	14	8.0%	20	6	3.4%	11	6.3%	17
< 15,000	3	1.7%	19	10.8%	22	3	1.7%	17	9.7%	20
15,000–30,000	9	5.1%	20	11.4%	29	10	5.7%	15	8.5%	25
30,000–44,999	17	9.7%	21	11.9%	38	12	6.8%	27	15.3%	39
45,000	141	80.1%	102	58.0%	243	145	82.4%	106	60.2%	251
Body Mass Index										
Missing	2	1.1%	1	0.6%	3	1	0.6%	3	1.7%	4
< 18.5	8	4.5%	13	7.4%	21	12	6.8%	15	8.5%	27
18.5–24.9	119	67.6%	105	59.7%	224	112	63.6%	104	59.1%	216
25–29.9	38	21.6%	39	22.2%	77	39	22.2%	38	21.6%	77
30	9	5.1%	18	10.2%	27	12	6.8%	16	9.1%	28

Table 2

Odds Ratio for Risk of Birth Defects According to Maternal Dietary Glycemic Intake, United States and Canada, 1988–1998

Birth Defect	Spline Cut-off		Adjusted ^a OR based on spline	
	N	%	OR	95%CI
Amniotic Bands (N=48)				
Dietary Glycemic Index	Cut-off at 62			
Cases	7	14.6%	3.01	1.1, 8.1
Control	37	5.3%		
Dietary Glycemic Load	Cut-off at 196			
Cases	3	6.3%	1.27	0.2, 6.7
Control	25	3.6%		
Anorectal Defects (N= 160)				
Dietary Glycemic Index	Cut-off at 60			
Cases	37	23.1%	1.54	1.0, 2.5
Controls	102	12.5%		
Dietary Glycemic Load	Cut-off at 192			
Cases	17	10.6%	2.35	1.1, 4.9
Controls	32	4.6%		
Craniosynostosis (N=189)				
Dietary Glycemic Index	Cut-off at 61			
Cases	24	12.7%	1.79	1.0, 3.2
Controls	59	8.4%		
Dietary Glycemic Load	Cut-off at 210			
Cases	4	2.1%	3.18	0.8, 13.3
Controls	9	1.3%		
Gastroschisis (N=78)				
Dietary Glycemic Index	Cut-off at 63			
Cases	2	2.6%	0.38	0.0, 3.4
Controls	19	2.7%		
Dietary Glycemic Load	None identified ^b			
Hypospadias (N=241)				
Dietary Glycemic Index	Cut-off at 63			
Cases	9	3.7%	1.89 ^c	0.7, 5.1
Controls (males only)	7	2.0%		
Dietary Glycemic Load	None identified			
Limb Reduction (N=183)				
Dietary Glycemic Index	None identified			
Dietary Glycemic Load	Cut-off at 224			
Cases	2	1.1%	2.58	0.3, 22.4
Control	3	0.4%		

Birth Defect	Spline Cut-off		Adjusted ^a OR based on spline	
	N	%	OR	95%CI
Omphaloceles (N=115)				
Dietary Glycemic Index	None identified			
Dietary Glycemic Load	None identified			
Orofacial Clefts (N=626)				
Dietary Glycemic Index	Cut-off at 62			
Cases	43	6.9%	1.24	0.7, 2.1
Control	35	5.0%		
Dietary Glycemic Load	Cut-off at 227			
Cases	7	1.1%	2.22	0.4, 11.4
Control	2	0.3%		
Renal Agenesis (N= 47)				
Dietary Glycemic Index	Cut-off at 58			
Cases	18	38.3%	1.08	0.6, 2.1
Control	246	34.9%		
Dietary Glycemic Load	None identified			
Small Intestinal Defects (N=79)				
Dietary Glycemic Index	Cut-off at 62			
Cases	7	9.0%	2.04	0.8, 4.9
Controls	37	5.0%		
Dietary Glycemic Load	None identified			
Tracheoesophageal Fistulas (N=168)				
Dietary Glycemic Index	Cut-off at 64			
Cases	2	1.2%	0.32	0.0, 2.8
Control	11	1.6%		
Dietary Glycemic Load	Cut-off at 230			
Cases	2	1.2%	7.29	0.6, 84.1
Control	1	0.1%		

^a Adjusted OR adjust for maternal race, maternal age, center, income, and fiber (in GL models only)

^b No diverging effect was visible in the spline therefore no cut-off points were identified

^c Crude results presented due to adjusted models being unstable

Table 3

Odds Ratio for Risk of Isolated Birth Defects According to Maternal Glycemic Intake, United States and Canada, 1988–1998

Birth Defect	Spline Cut-off		Adjusted ^a OR based on spline	
	N	%	OR	95%CI
Amniotic Bands (N=40)				
Dietary Glycemic Index	Cut-off at 62			
Cases	7	17.5%	3.95	1.4, 10.8
Control	37	5.3%		
Dietary Glycemic Load	Cut-off at 196			
Cases	3	7.5%	1.53	0.3, 8.2
Control	25	3.6%		
Anorectal Defects(N=70)				
Dietary Glycemic Index	Cut-off at 60			
Cases	15	21.4%	1.55	0.8, 3.1
Control	102	14.5%		
Dietary Glycemic Load	Cut-off at 192			
Cases	7	10.0%	2.42	0.8, 6.9
Control	32	4.6%		
Craniosynostosis (N=160)				
Dietary Glycemic Index	Cut-off at 61			
Cases	18	11.3%	1.52	0.8, 2.9
Control	59	8.4%		
Dietary Glycemic Load	Cut-off at 210			
Cases	4	2.5%	3.82	0.9, 15.9
Control	9	1.3%		
Gastroschisis (N=67)				
Dietary Glycemic Index	Cut-off at 63			
Cases	2	3.0%	0.4	0.0, 3.7
Controls	19	2.7%		
Dietary Glycemic Load	None identified ^b			
Hypospadias (N= 180)				
Dietary Glycemic Index	Cut-off at 63			
Cases	8	4.4%	2.27 ^c	0.8, 6.4
Controls (males only)	7	2.0%		
Dietary Glycemic Load	None identified			
Limb Reduction (N=95)				
Dietary Glycemic Index	None identified			
Dietary Glycemic Load	None identified			
Omphaloceles (N=66)				
Dietary Glycemic Index	None identified			

Birth Defect	Spline Cut-off		Adjusted ^a OR based on spline	
	N	%	OR	95%CI
Dietary Glycemic Load	None identified			
Orofacial Clefts (N=517)				
Dietary Glycemic Index	Cut-off at 62			
Cases	34	6.6%	1.23	0.7, 2.1
Control	35	5.0%		
Dietary Glycemic Load	Cut-off at 227			
Cases	5	1.0%	1.66	0.3, 9.3
Control	2	0.3%		
Small Intestinal Defects (N=52)				
Dietary Glycemic Index	Cut-off at 62			
Cases	4	7.7%	1.50 ^c	0.5, 4.4
Control	37	5.3%		
Dietary Glycemic Load	None identified			
Tracheoesophageal Fistulas (N=67)				
Dietary Glycemic Index	None identified			
Dietary Glycemic Load	Cut-off at 230			
Cases	1	1.5%	10.71 ^c	0.6, 178.0
Control	1	0.1%		

^a Adjusted OR adjust for maternal race, maternal age, center, income, and fiber (in GL models only)

^b No diverging effect was visible in the spline therefore no cut-off points were identified

^c Crude results presented due to adjusted models being unstable