Neural tube defects associated with maternal periconceptional dietary intake of simple sugars and glycemic index[1–3]

Gary M Shaw, Thu Quach, Verne Nelson, Suzan L Carmichael, Donna M Schaffer, Steve Selvin, and Wei Yang

ABSTRACT

Background: Maternal diabetes, prepregnancy obesity, hyperinsulinemia, and intakes of sweets have been associated with increased risks of neural tube defects (NTDs). The interdependence of these factors suggests a common pathogenesis via altered glycemic control and insulin demand.

Objective: We investigated whether maternal periconceptional dietary intakes of sucrose, glucose, fructose, and foods with higher glycemic index values influence the risk of having NTD-affected pregnancies.

Design: In a population-based case-control study, all hospitals in 55 of the 58 counties in California participated. In-person interviews were conducted with the mothers of 454 NTD cases (including fetuses and infants who were electively terminated, stillborn, or born alive) and with the mothers of 462 nonmalformed controls within an average of 5 mo from the term delivery date. The risk of having an NTD-affected pregnancy was the main outcome measure.

Results: Risks of having an NTD-affected pregnancy were not substantially elevated in relation to periconceptional intakes of glucose or fructose. Elevated risks of ≈2-fold were observed for higher intakes of sucrose and foods with higher glycemic index values. Elevated risks were observed for high sucrose intake irrespective of whether adjustment was made for other covariates such as maternal folic acid intake. For higher glycemic index values, adjusted elevated risks of ≥ 4-fold were observed in women whose body mass index (in kg/m^2) was > 29.

Conclusion: Our observed associations support observations that potential problems in glucose control are associated with NTD risk even among nondiabetic women. *Am J Clin Nutr* 2003;78: 972–8.

INTRODUCTION

Maternal nutritional factors are implicated in the complex etiology of neural tube defects (NTDs). Foremost among these factors is the role of periconceptional folic acid intake in reducing women's risks of having NTD-affected pregnancies (1, 2(). Other nutritional factors have also been observed to influence risks of NTD-affected pregnancies. For example, increased intakes of methionine (3), zinc (4), vitamin C (5), and dairy products (6) are associated with decreased NTD risks. Other maternal factors such as diabetes (7), prepregnancy obesity (8–10), hyperinsulinemia (11), and intakes of sweets (12) are associated with increased NTD risks. The interdependence of these latter factors led us to hypothesize that intakes of sucrose, glucose, and fructose might influence NTD risk through a common pathway of altered glycemic control and insulin demand. We hypothesized that women who had higher dietary intakes of these sugars and women with a higher glycemic index (a classification of foods according to glycemic responses) would have an elevated risk of NTD-affected pregnancies. Thus, we examined data from a large population-based case-control study to investigate whether maternal periconceptional (3 mo before to 3 mo after conception) dietary intakes of sucrose, glucose, fructose, and foods with higher glycemic index values influenced the risk of having an NTD-affected pregnancy.

SUBJECTS AND METHODS

Details of the population-based case-control study used in this analysis were described previously (13). Briefly, infants and fetuses with NTDs (anencephaly, spina bifida cystica, craniorachischisis, or iniencephaly) were ascertained by reviewing the medical records, including ultrasonographic records, of all the infants and fetuses delivered in all the hospitals and genetic clinics in select California counties by women who reported their residence as being in California. Among the cohort of 708 129 births and fetal deaths that occurred between June 1989 and May 1991, singleton liveborn infants, fetal deaths, and fetuses that were prenatally diagnosed and electively terminated were eligible for inclusion in the study. Six hundred fifty-three singleton infants and fetuses were ascertained as having an eligible NTD diagnosis. Controls were randomly selected from each area hospital in proportion to the hospital's estimated contribution to the total population of infants who were born alive in a given month from June 1989 to May 1991. The controls consisted of 644 singleton infants who were born without a reportable congenital anom-

[1] From the March of Dimes Birth Defects Foundation, California Birth Defects Monitoring Program, Berkeley, CA (GMS, VN, SLC, and WY); the California Department of Health Services, Oakland, CA (TQ); Kaiser Permanente, Oakland, CA (DMS); and the University of California, Berkeley (SS).

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[3] Address reprint requests to GM Shaw, California Birth Defects Monitoring Program, 1917 Fifth Street, Berkeley, CA 94710. E-mail: gsh@cbdmp.org.

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aly. The study was approved by the California State Committee for the Protection of Human Subjects.

Women who spoke only languages other than English or Spanish or who had a previous NTD-affected pregnancy were excluded from the study, which left 613 cases and 611 controls. In-person interviews with the mothers of 538 (87.8%) cases and 539 (88.2%) controls were completed an average of 4.9 and 4.6 mo after the actual or projected date of term delivery for the cases and the controls, respectively. Medical histories, reproductive histories, and information about activities associated with various lifestyles primarily during the periconceptional period (6-mo period from 3 mo before to 3 mo after conception) were elicited from the women.

The 100-item food-frequency questionnaire developed by Block et al (14) was used to assess nutrient intakes from the diet. This instrument has been validated for use in epidemiologic studies (15–17). For example, comparisons between 4-d diet records and this particular food-frequency questionnaire showed correlation coefficients ranging from 0.47 for vitamin A to 0.67 for percentage of calories from fat, with a correlation coefficient of 0.51 for percentage of energy from carbohydrates (17). The women who participated in the study completed the questionnaire (in English or Spanish) themselves while interviewers were present to assist them. Each woman was instructed to estimate her usual frequency and portion size of the food items she consumed during the 3 mo before conception. Average daily intake of nutrients was computed by using the questionnaire's software (14). Of the 1077 women who completed an in-person interview, 1007 completed a food-frequency questionnaire; of these, 916 women provided data that were suitable on the basis of error checks built into the analytic software (14). The analytic program examined the data for various errors to produce invalid data; more than one-half of the excluded questionnaires were excluded because the number of foods selected for daily consumption was considered excessive. Of the 916 women with suitable data, 454 were mothers of NTD cases and 462 were mothers of controls. The 454 cases consisted of 177 with anencephaly, 256 with spina bifida, and 21 with other NTD phenotypes.

The glucose, fructose, and sucrose composition of individual foods was added to the nutrient database by using values made available to us by another group of investigators (E Mayer-Davis, personal communication, 2001; reference 18). Average daily intakes of each of these sugars were estimated from the women's questionnaire responses by considering portion size and frequency of consumption of each food item.

For all the 916 mothers who provided dietary data, we estimated the average glycemic index values of their consumed foods. Glycemic index values do not reflect inherent qualities of foods but are a quantitative assessment of the metabolic response, ie, blood glucose and insulin, to a given food compared with that to a standard (19–21).

Our glycemic index values were based on glucose as the standard. The values for most foods were adopted directly from the nutrient database developed for use with the Willett food-frequency questionnaire (22–24). Several food items on our list consisted of groups of foods or mixed dishes, the components of which were available on the food (Willett) list. In the case of grouped items (eg, donuts, cookies, cake), the relative frequency of consumption was used to estimate the contribution of the food to the group. Thus, the glycemic index value derived for the group was the average of the values for each food weighted in accordance with its relative consumption [in the NHANES (National Health and Nutrition Examination Survey) population, from which the food group was derived]. Similarly, the glycemic index value for each component of a mixed dish was weighted according to the relative composition of that component in the mixed dish (on the basis of the recipe), and the values of all the individual components were then averaged to derive a single glycemic index value for the mixed dish. In the few instances in which no corresponding food item was found on the food list, the glycemic index value of a food comparable in calories, carbohydrates, sucrose, fat, and dietary fiber was used. These are similar procedures to those used by the Willett group to impute glycemic index values for foods for which no values were available in the literature. The few foods for which no comparable foods were included in the food list or that did not contain carbohydrates were not assigned a glycemic index value.

An average dietary glycemic index was computed for the mother of each case and control. This computation followed the approach suggested by Wolever et al (23) that has been used by others (25). Briefly,

$$\begin{aligned}\text{Average glycemic index} &= [\text{sum (carbohydrate content per serving of each food)} \\ &\times \text{(average daily number of servings of the specific food)} \\ &\times \text{(glycemic index of the specific food)}]/ \\ &\text{(total daily carbohydrate intake)} \quad (1)\end{aligned}$$

NTD risk was estimated by using logistic regression models. Odds ratios and 95% CIs were computed to summarize the potential influence of several possible risk factors. Models were constructed to assess effects associated with continuous intakes of glucose, fructose, and sucrose and continuous glycemic index values. Models in which intakes and glycemic index values were considered according to quartile cutoffs were also constructed. Values for intakes and glycemic index among the mothers of the controls were used to establish the quartiles for each measure. For quartile analyses, odds ratios and 95% CIs were computed to estimate risk, with the lowest quartile as the reference. Maternal race or ethnicity (Latina, foreign-born; Latina, US-born; white, non-Latina; black; other), education ($<$ high school graduate, high school graduate, $>$ high school graduate), height, prepregnant weight, body mass index (BMI; in kg/m^2), energy intake (kcal/d), dietary folate intake (μg/d), and periconceptional vitamin supplementation (none, use in the 3 mo before conception, use beginning in the 3 mo after conception) were considered as covariates in the analyses. Frequencies and mean values for these variables are shown in **Table 1**. Other variables that were investigated but were found to not substantially influence NTD risk included maternal age and gravidity (data for these variables are also shown in Table 1). All analyses were performed by using SAS (26).

An additional potential covariate that was considered in some analyses of glycemic index values was a measure of the women's physical activity. We previously observed that increased physical activity may decrease NTD risk (27). Our analyses included an index of physical activity that reflected

TABLE 1
Characteristics of women who did (cases) or did not (controls) have pregnancies affected by neural tube defects[1]

	Cases (n = 454)	Controls (n = 462)
Race or ethnicity [n (%)]		
White	196 (43.2)	249 (54.0)
US-born, Latina	58 (12.8)	67 (14.5)
Foreign-born, Latina	156 (34.4)	93 (20.2)
Other	44 (9.7)	52 (11.3)
Education [n (%)]		
<High school graduate	169 (37.3)	115 (25.0)
High school graduate	177 (39.1)	198 (43.0)
>High school graduate	107 (23.6)	148 (32.1)
Multivitamin use [n (%)]		
None	167 (37.1)	122 (26.9)
Began 3 mo before conception	75 (16.7)	84 (18.5)
Began in first trimester	208 (46.2)	247 (54.5)
Gravidity [n (%)]		
1	107 (23.6)	93 (20.1)
2	117 (25.8)	142 (30.7)
3	102 (22.5)	99 (21.4)
>3	128 (28.2)	128 (27.7)
Age (y)	26.4 ± 5.8[2]	27.5 ± 5.7
Height (m)	1.6 ± 0.08	1.6 ± 0.08
Prepregnancy weight (kg)	64.1 ± 15.9	60.9 ± 12.0
BMI (kg/m^2)	24.7 ± 5.8	23.0 ± 4.3
Energy intake (kcal/d)	2243.0 ± 886.3	2384.3 ± 945.0
Dietary folate intake (μg/d)	351.8 ± 184.8	374.5 ± 199.5

[1] Percentages may not equal 100 because of missing data or rounding.
[2] $\bar{x}$ ± SD.

the reported frequency of and estimated exertion levels for 6 types of activity. For our analyses, the index was divided into 2 categories: one for women who rarely, if ever, engaged in physical activity and one for women who routinely engaged in various levels of physical activity during the periconceptional period. Details of this approach can be found elsewhere (27).

RESULTS

Risks of NTD-affected pregnancies were not significantly elevated in relation to periconceptional intakes (adjusted for energy intake) of glucose or fructose, irrespective of whether intakes were analyzed as continuous or discrete (quartiles) measures (**Table 2**), but did appear to be modestly elevated for higher intakes of sucrose. Computed odds ratios were not substantially influenced by simultaneously controlling for energy intake, maternal race or ethnicity, education level, periconceptional vitamin use, height, prepregnancy weight, or dietary folate intake (Table 2). For intakes of the 3 sugars, analyses specific to NTD phenotype, ie, anencephaly or spina bifida, did not show a substantially different pattern of effect from that observed for all NTDs combined, although estimates were slightly higher for spina bifida than for anencephaly (data not shown).

Elevated risks of NTDs were observed for maternal intakes of foods having higher glycemic index values (**Table 3**). This pattern was observed for all NTDs, spina bifida, and anencephaly in analyses adjusted only for energy intake. Multivariate analyses showed a strong interaction between maternal prepregnancy weight and maternal glycemic index on NTD risk (P = 0.009) and between maternal prepregnancy BMI and maternal glycemic index on NTD risk (P = 0.025). Thus, we stratified subsequent analyses according to 2 maternal BMI categories: ≤ 29 and > 29. We adjusted for the following covariates: maternal education, race or ethnicity, periconceptional vitamin use, dietary folate intake, and total energy intake. Elevated risks of NTDs for higher glycemic index values were observed in unadjusted analyses within both BMI categories (**Tables 4** and **5**). However, adjusted analyses showed different results (Tables 4 and 5). We did not observe elevated risks of NTDs for higher glycemic index values in the women whose BMI was ≤ 29, whereas we did observe elevated risks (4–5-fold) associated with higher glycemic index values in the women whose BMI was > 29 (ie, the obese group) (Table 5). The risks were highest for spina bifida. The observed effects were not influenced by removing 21 mothers of cases and 34 mothers of controls who had a history of diabetes (5 mothers of cases and 4 mothers of controls who had type 1 or 2 diabetes and 16 mothers of cases and 30 mothers of controls who had gestational diabetes), nor were risks substantially changed in analyses that adjusted for maternal periconceptional physical activity (data not shown).

DISCUSSION

Our results indicate elevated NTD risks associated with maternal intakes of periconceptional diets having higher glycemic index values and higher sucrose content but do not indicate elevated risks associated with higher intakes of glucose and fructose. Controlling for the potential effects of maternal intakes of supplemental folic acid and dietary folate as well as for other potential covariates did not substantially reduce the risks associated with sucrose intake or with glycemic index, specifically among obese women. Intakes of foods with higher glycemic index values are predictive of elevated serum glucose concentrations and consequent increased insulin demand and hyperinsulinemia (24, 28–31). Such foods include highly processed grains, monosaccharides, and disaccharides, whereas carbohydrates with low glycemic index values include unprocessed whole grains, beans, fruits, vegetables, and some dairy products. The reason for elevated risks for sucrose intake but not for glucose and fructose intakes is unknown. Glucose and fructose intakes may be too subtle a measure to observe changes in NTD risk.

Associations with higher glycemic index values have been observed for diseases such as colon cancer (32) and diabetes mellitus (24, 25). In addition, elevated serum glucose concentrations and increased total sugar intakes among pregnant women are associated with adverse reproductive outcomes, such as preterm delivery, pregnancy complications, macrosomia, and low birth weight (33–36). We are not aware of any studies that investigated higher glycemic index values or elevated serum glucose concentrations as risk factors for congenital anomalies. Thus, this is the first study to find an association between NTD risk and glycemic index among nondiabetic women.

Our observation of an association between higher glycemic index, predominantly in obese women, and increased NTD risk extends observations that problems in glucose control may be associated with NTD risk. These observations include the following: *1*) an association between elevated prepregnancy BMI

TABLE 2
Effect estimates [odds ratios (ORs)] for neural tube defects associated with maternal intakes of glucose, sucrose, and fructose during the periconceptional period[1]

Sugar	Cases	Controls	OR (95% CI)[2]	Adjusted OR (95% CI)[3]
	n	*n*		
Sucrose				
Continuous measure[4]	454	462	1.02 (1.01, 1.02)	1.01 (1.01, 1.02)
P			0.001	0.003
Quartile measure (g)				
≤20.93	101	116	Ref —	Ref —
20.94–32.40	108	115	1.25 (0.85, 1.84)	1.45 (0.96, 2.19)
32.41–46.25	121	116	1.71 (1.14, 2.58)	1.51 (0.97, 2.34)
>46.25	124	115	2.37 (1.46, 3.85)	2.34 (1.39, 3.96)
Glucose				
Continuous measure[4]	454	462	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
P			0.229	0.049
Quartile measure (g)				
≤13.20	121	116	Ref —	Ref —
13.21–19.85	119	115	1.07 (0.74, 1.55)	1.11 (0.75, 1.64)
19.86–30.03	106	116	1.04 (0.70, 1.54)	1.18 (0.77, 1.79)
>30.03	108	115	1.23 (0.79, 1.92)	1.37 (0.84, 2.24)
Fructose				
Continuous measure[4]	454	462	1.00 (1.00, 1.01)	1.01 (0.99, 1.02)
P			0.296	0.103
Quartile measure (g)				
≤14.28	115	116	Ref —	Ref —
14.29–21.79	123	115	1.14 (0.79, 1.64)	1.19 (0.81, 1.77)
21.80–34.35	114	116	1.16 (0.78, 1.70)	1.28 (0.83, 1.95)
>34.35	102	115	1.19 (0.76, 1.87)	1.33 (0.82, 2.17)

[1] Quartiles were determined from intakes in the mothers of the controls. Ref, reference.
[2] Adjusted for maternal total energy intake.
[3] Adjusted for maternal weight, height, education, race or ethnicity, periconceptional vitamin use, dietary folate intake, and energy intake.
[4] OR expressed as change in risk per 1-g change in intake.

TABLE 3
Effect estimates [odds ratios (ORs)] for neural tube defects associated with maternal glycemic index values during the periconceptional period[1]

Glycemic index	Cases	Controls	OR (95% CI)[2]
	n	*n*	
All neural tube defects			
Continuous measure[3]	454	462	1.06 (1.03, 1.10)
P			0.005
Quartile measure			
≤50.77	85	115	Ref —
50.78–53.22	100	116	1.19 (0.81, 1.76)
53.23–55.56	112	115	1.33 (0.90, 1.95)
>55.56	157	116	1.86 (1.29, 2.70)
Spina bifida			
Continuous measure[3]	256	462	1.07 (1.02, 1.11)
P			0.002
Quartile measure			
≤50.77	46	115	Ref —
50.78–53.22	53	116	1.16 (0.72, 1.86)
53.23–55.56	61	115	1.34 (0.84, 2.12)
>55.56	96	116	2.11 (1.36, 3.27)
Anencephaly			
Continuous measure[3]	177	462	1.06 (1.01, 1.11)
P			0.020
Quartile measure			
≤50.77	36	115	Ref —
50.78–53.22	43	116	1.20 (0.71, 2.00)
53.23–55.56	44	115	1.22 (0.73, 2.04)
>55.56	54	116	1.48 (0.90, 2.42)

[1] Quartiles were determined from glycemic index values in the mothers of the controls. Ref, reference.
[2] Adjusted for maternal total energy intake.
[3] OR expressed as change in risk per 1-g change in intake.

TABLE 4
Effect estimates [odds ratios (ORs)] for neural tube defects associated with maternal glycemic index values during the periconceptional period in women whose BMI (in kg/m^2) was ≤ 29[1]

Glycemic index	Cases	Controls	OR (95% CI)[2]	Adjusted OR (95% CI)[3]
	n	*n*		
All neural tube defects				
Continuous measure[4]	352	404	1.05 (1.01, 1.09)	1.02 (0.98, 1.06)
P			0.013	0.405
Quartile measure				
≤50.77	76	105	Ref —	Ref —
50.78–53.22	80	102	1.10 (0.72, 1.66)	0.98 (0.64, 1.50)
53.23–55.56	85	104	1.14 (0.76, 1.73)	0.93 (0.60, 1.43)
>55.56	111	93	1.68 (1.12, 2.53)	1.30 (0.84, 2.00)
Spina bifida				
Continuous measure[4]	194	404	1.05 (1.00, 1.09)	1.02 (0.97, 1.07)
P			0.062	0.512
Quartile measure				
≤50.77	41	105	Ref —	Ref —
50.78–53.22	44	102	1.11 (0.67, 1.85)	0.99 (0.59, 1.65)
53.23–55.56	47	104	1.17 (0.71, 1.93)	0.99 (0.59, 1.65)
>55.56	62	93	1.75 (1.08, 2.85)	1.39 (0.83, 2.33)
Anencephaly				
Continuous measure[4]	145	404	1.05 (1.00, 1.11)	1.01 (0.96, 1.07)
P			0.046	0.717
Quartile measure				
≤50.77	33	105	Ref —	Ref —
50.78–53.22	34	102	1.06 (0.61, 1.84)	0.97 (0.55, 1.72)
53.23–55.56	34	104	1.05 (0.61, 1.83)	0.86 (0.48, 1.55)
>55.56	44	93	1.50 (0.88, 2.56)	1.08 (0.60, 1.95)

[1] Quartiles were determined from glycemic index values in the mothers of the controls. Ref, reference.
[2] Adjusted for maternal total energy intake.
[3] Adjusted for race or ethnicity, vitamin use, energy intake, and dietary folate intake.
[4] OR expressed as change in risk per 1-g change in intake.

TABLE 5
Effect estimates [odds ratios (ORs)] for neural tube defects associated with maternal glycemic index values during the periconceptional period in women whose BMI (in kg/m^2) was > 29[1]

Glycemic index	Cases	Controls	OR (95% CI)[2]	Adjusted OR (95% CI)[3]
	n	*n*		
All neural tube defects				
Continuous measure[4]	73	39	1.12 (1.01, 1.25)	1.17 (1.03, 1.32)
P			0.039	0.017
Quartile measure				
≤50.77	8	9	Ref —	Ref —
50.78–53.22	16	10	1.98 (0.56, 7.01)	2.61 (0.64, 10.66)
53.23–55.56	20	7	3.19 (0.87, 11.72)	5.74 (1.32, 24.90)
>55.56	29	13	2.64 (0.81, 8.59)	4.05 (1.04, 15.73)
Spina bifida				
Continuous measure[4]	46	39	1.13 (1.01, 1.27)	1.16 (1.01, 1.34)
P			0.038	0.033
Quartile measure				
≤50.77	5	9	Ref —	Ref —
50.78–53.22	7	10	1.31 (0.30, 5.67)	2.05 (0.37, 11.29)
53.23–55.56	12	7	3.13 (0.74, 13.25)	6.83 (1.23, 38.04)
>55.56	22	13	3.15 (0.86, 11.57)	5.62 (1.14, 27.61)
Anencephaly				
Continuous measure[4]	22	39	1.08 (0.93, 1.24)	1.21 (0.96, 1.52)
P			0.319	0.108
Quartile measure				
≤50.77	3	9	Ref —	Ref —
50.78–53.22	7	10	2.64 (0.47, 14.78)	1.22 (0.15, 9.69)
53.23–55.56	6	7	1.75 (0.29, 10.39)	1.73 (0.21, 14.27)
>55.56	6	13	1.25 (0.23, 6.89)	1.89 (0.21, 17.38)

[1] Quartiles were determined from glycemic index values in the mothers of the controls. Ref, reference.
[2] Adjusted for maternal total energy intake.
[3] Adjusted for race or ethnicity, vitamin use, energy intake, and dietary folate intake.
[4] OR expressed as change in risk per 1-g change in intake.

and an increased risk of having NTD-affected pregnancies (8–10), combined with observations that increasing BMI is predictive of elevated glucose concentrations in nondiabetic women (37); *2*) increased risks of NTD-affected pregnancies among diabetic women (7); and *3*) an association between hyperinsulinemia and an increased risk of delivering infants with NTDs (11).

The early embryo is believed not to have pancreatic function until the development of β cells after week 7 of gestation (38). Thus, at the time of neural tube closure (approximately week 4 of gestation), embryos could theoretically receive excess glucose from the mother and be unable to regulate the excess. Inferences drawn from both human and experimental studies have indicated that markedly elevated glucose concentrations in mothers probably contribute to the development of congenital anomalies (38). Conversely, it is possible that maternal hyperglycemia may be followed by hypoglycemia, whereby the fetus experiences a lack of glucose. Substantially lowered glucose concentrations have been observed to have teratogenic properties in vitro (39).

Mechanistically, elevated glucose concentrations in experimental systems lead to oxidative stress and embryonic depletion of inositol (40), and the latter is implicated in abnormal closure of the developing neural tube in experimental studies (41, 42). Experimental evidence also suggests that inhibited inositol uptake due to an elevated glucose concentration may underlie the relation between maternal diabetes and congenital anomalies in offspring (43). Whether an inositol-related mechanism is active in human NTD development is unknown.

Despite the present study's population-based ascertainment of cases and controls, high maternal participation rate, large sample size, and ability to control for many relevant covariates, the ability of the study to draw firm inferences is limited by the qualitative, ie, surrogate, nature of the glycemic index to reflect measures of serum glucose concentration, particularly at the relevant embryologic time. However, errors that might arise as a result of not having actually measured serum glucose concentrations would probably be the same in both the mothers of cases and the mothers of controls. Therefore, such misclassification errors would probably produce attenuated, rather than inflated, estimates of NTD risks. Moreover, the epidemiologic use of the glycemic index has been established in studies of diabetes (24), and the methodologic implications of the index, including its ability to predict the glycemic effect of the carbohydrate content of the individual foods that constitute mixed meals (19, 44), are well described.

In interpreting our findings, we cannot exclude the possibility that the observed elevated risks were attributable to recall bias. Although there is little evidence that recall bias contributes substantially to the results of studies such as these (45), it is possible, for example, that the mothers of the cases overreported or the mothers of the controls underreported intakes of foods associated with a higher glycemic index. However, because most of the women in the study were probably unaware of the glycemic index values of the foods they ate, it seems unlikely that differential recall between the mothers of the cases and the mothers of the controls is a likely explanation of our results. We also cannot exclude the possibility that the observed elevated risks were due to random variation or were obtained as a result of many comparisons conducted in the data set.

It has been suspected for nearly 20 y that control of glucose metabolism in early pregnancy lowers the risks of congenital anomalies (46). On the basis of some experimental model systems (47), it has also been suspected for many years that insulin may not exert a direct teratogenic effect. In addition, both maternal hyperinsulinemia (11) and hyperglycemia (48) have been suggested to influence NTD risk. Thus, our finding of a quadrupling or more of NTD risk among nondiabetic obese women who consume foods that have high glycemic potential offers one more supporting clue toward understanding the complex etiology of NTDs.

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