

Greater Maternal Weight and the Ongoing Risk of Neural Tube Defects After Folic Acid Flour Fortification

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OBJECTIVE: Maternal obesity is likely a risk factor for neural tube defects (NTDs). By late 1997, it became mandatory in Canada that all refined wheat flour be fortified with folic acid. Because overweight women may consume greater quantities of refined wheat flour, we questioned whether their risk of NTD changed after flour fortification.

METHODS: A retrospective population-based study was conducted between 1994 and late 2000. We included all Ontarian women who underwent antenatal maternal screening at 15 to 20 weeks of gestation. Self-declared maternal date of birth, ethnicity, current weight, and the presence of pregestational diabetes mellitus were recorded in a standardized fashion on the maternal screening requisition sheet. The presence of NTDs was systematically detected both antenatally and postnatally. The risk of open NTD was evaluated across maternal weight quartiles and deciles, and an interaction between greater maternal weight and the presence of flour fortification was tested using multiple logistic regression analysis.

RESULTS: A total of 292 open NTDs were detected among 420,362 women. The adjusted odds ratio (OR) for NTD was 1.2 (95% confidence interval [CI] 1.1–1.3) per 10-kg incremental rise in maternal weight. Comparing the highest with the lowest quartile of maternal weight, the adjusted OR for NTD was 2.6 (95% CI 1.8–4.0). A similar finding was observed for the highest compared with lowest weight deciles (adjusted OR 3.3, 95% CI 1.7–6.2). The interaction between elevated maternal weight and the presence of folic acid flour fortification was of borderline significance ($P =$

.09). Before fortification, greater maternal weight was associated with a modestly increased risk of NTD (adjusted OR 1.4, 95% CI 1.0–1.8); after flour fortification, this effect was more pronounced (adjusted OR 2.8, 95% CI 1.2–6.6).

CONCLUSION: These data emphasize the higher risk of NTD associated with increased maternal weight, even after universal folic acid flour fortification. Beyond periconceptional folic acid use, consideration should be given to testing whether prepregnancy weight reduction is an independent means of preventing NTD. (*Obstet Gynecol* 2005;105:261–5. © 2005 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: II-2

Maternal obesity is likely one of several risk factors for neural tube defects (NTDs)^{1–3}. Greater mean daily consumption of sucrose-containing and high-glycemic index foods was recently shown to be associated with an increased risk of NTD, especially among obese women.⁴ At the same time, greater physical activity was associated with a lower risk of NTD.⁵ Commercially available white-wheat-flour breads and cereals have a high glycemic index, a standardized measure of the postprandial rise in serum glucose concentrations per 50 g of carbohydrate,⁶ and are associated with a higher risk of obesity⁷ and non-insulin-dependent diabetes mellitus.⁸

Randomized clinical trials have demonstrated at least a 50% reduction in the relative risk of NTD with periconceptional folic acid supplement use.⁹ Moreover, after the introduction of mandatory folic acid fortification of all refined wheat flour milled in the United States and Canada in late 1997, an impressive decline was observed in the prevalence of open NTDs,^{10–12} along with a significant rise in blood folate concentrations.¹³

Women who ingest greater quantities of white-wheat-flour foods before conception are at increased risk for obesity¹⁴ and, perhaps, fetal NTD.⁴ At the same time, these individuals would be expected to ingest greater quantities of folic acid than nonobese women in the

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context of fortification. We examined whether the risk of open NTD, in relation to maternal obesity, changed after the introduction of Canada's folic acid fortification program.

METHODS

We performed a retrospective population-based study and included all Ontarian women who underwent antenatal maternal screening between 1994 and late 2000, as described elsewhere.¹¹ Briefly, since 1993, standardized maternal screening was made available to all women at 15 to 20 weeks of gestation through a physician or midwife, with a mean rate of use of more than 70%. Self-declared maternal date of birth, ethnicity, weight, and the presence of pregestational diabetes mellitus were recorded in a standardized fashion on the maternal screening requisition sheet, completed at the time of screening. Open NTD cases were detected antenatally by ultrasonography or fetal autopsy, or postnatally through data linkage of the mother's Ontario health insurance number with that of her infant during the delivery hospitalization through the Canadian Institute for Health Information Discharge Abstract Database.¹¹

Means and standard deviations (SDs) were computed and compared using an unpaired *t* test. The trend in the prevalence of open NTD across maternal weight quartiles (Q1–Q4) and deciles (D1–D10), respectively, was evaluated using a Mantel χ^2 test.¹⁵ Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were derived from logistic regression analysis, with Q1 and D1 as the respective referents. We adjusted for maternal age (1-year increments), maternal race (Black, Asian, Hispanic or First Nations [Native North American], or Other compared with White), pregestational diabetes, and year of screening. The same model was used to examine the effect of maternal weight in 10-kg increments on the associated risk of NTD. Logistic regression analysis was also used to test for a significant interaction term between high maternal weight (ie, greater than Q4 compared with Q1–Q3) and folic acid food fortification (ie, before compared with after January 1998).¹¹ Finally, we compared the risk of NTD before and after fortification, stratified by weight quartile, adjusting for maternal age, ethnicity, and pregestational diabetes mellitus; the corresponding relative odds reduction was calculated as $[(1 - \text{OR}) \times 100]$.

All variables were included in the model a priori, and statistical significance was set at a 2-tailed $P < .05$. Analyses were performed using SAS 8.0 (SAS Institute, Cary, NC). The study was done in accordance with a research protocol approved through the Ministry of Health and Long-term Care in Ontario, as well as the

Table 1. Participant Characteristics

Maternal Characteristic	Open Neural Tube Defect in Fetus or Infant	
	Present (n = 292)	Absent (n = 420,070)
Mean (\pm SD) age, yr	29.3 (\pm 5.5)	30.1 (\pm 5.1)
Mean (\pm SD) weight, kg	70.8 (\pm 15.6)	66.9 (\pm 14.4)
Pregestational diabetes mellitus, n (%)	4 (1.4)	2065 (0.5)
Ethnicity, n (%)		
White	221 (80.1)	290,578 (71.7)
Asian	38 (13.8)	77,022 (19.0)
Black	11 (4.0)	25,955 (6.4)
Other	1 (0.4)	10,008 (2.5)
First Nations*	5 (1.8)	1546 (0.4)

SD, standard deviation.

* Native North American.

Research Ethics Board of St. Michael's Hospital, and participant identifiers were removed from the data set before analysis.

RESULTS

A total of 420,362 women underwent maternal screening during the period of study, of whom 406,191 (97%) had available weight data (Table 1). The characteristics of the women with and without an NTD-affected pregnancy are presented in Table 1. Of 292 reported NTDs, 213 (73.0%) were identified antenatally. Women with an NTD-affected pregnancy had a greater mean weight \pm SD (70.8 \pm 15.6 kg) than unaffected mothers (66.9 \pm 14.4 kg), a difference of 3.9 kg (95% CI 2.2–5.6; $P < .001$) (Table 1).

For each 10-kg increase in maternal weight, the crude and adjusted odds ratios were 1.2 (95% CI 1.1–1.3). There was a significant trend in the rate of NTDs according to weight quartiles ($P < .001$) and deciles ($P < .001$) (Table 2, Fig. 1). The associated risk for an NTD was significantly higher in each of the upper 3 quartiles, relative to a Q1 weight less than 57.1 kg, and was most pronounced for a Q4 weight more than 73.6 kg (adjusted OR 2.1, 95% CI 1.4–3.2) (Table 2). When maternal body weight was divided into deciles, there was again a significantly higher associated risk of NTD in the upper deciles, especially the highest category of maternal weight greater than 85.6 kg (adjusted OR 3.3, 95% CI 1.7–6.2) (Table 2, Fig. 1).

The interaction term between elevated maternal weight and the presence of folic acid flour fortification was of borderline significance ($P = .09$). Before fortification, a maternal weight at Q4 or greater was associated with a slightly increased risk of NTD (adjusted OR 1.4, 95% CI 1.0–1.8), whereas after fortification, the risk was more pronounced (adjusted OR 2.8, 95% CI 1.2–6.6)



Table 2. Risk of Open Neural Tube Defects in Relation to Maternal Weight at 15 to 20 Weeks of Gestation

Maternal Weight, kg (n)	Neural Tube Defects*		
	n. (rate per 1,000)	Crude OR (95% CI)	Adjusted OR† (95% CI)
By quartiles			
Q1: < 57.1 (101,560)	38 (0.37)	1.0 (reference)	1.0 (reference)
Q2: 57.1–64.1 (101,513)	80 (0.79)	2.1 (1.4–3.1)	2.1 (1.4–3.2)
Q3: 64.2–73.5 (102,040)	69 (0.68)	1.8 (1.2–2.7)	2.0 (1.3–3.0)
Q4: > 73.6 (101,078)	94 (0.93)	2.5 (1.7–3.6)	2.6 (1.8–4.0)
By deciles			
D1: < 52.0 (40,629)	14 (0.34)	1.0 (ref)	1.0 (ref)
D2: 52.0–55.3 (41,695)	17 (0.41)	1.2 (0.58–2.4)	1.1 (0.54–2.3)
D3: 55.4–58.5 (40,981)	29 (0.71)	2.0 (1.1–3.9)	1.9 (0.96–3.6)
D4: 58.6–61.2 (41,213)	27 (0.66)	1.9 (1.0–3.6)	1.9 (1.0–3.8)
D5: 61.3–64.1 (38,555)	31 (0.80)	2.3 (1.2–4.4)	2.2 (1.1–4.2)
D6: 64.2–67.4 (40,502)	20 (0.49)	1.4 (0.72–2.8)	1.5 (0.74–3.0)
D7: 67.5–71.3 (40,260)	30 (0.74)	2.2 (1.1–4.1)	2.2 (1.2–4.3)
D8: 71.4–76.6 (41,011)	38 (0.93)	2.7 (1.5–5.0)	2.8 (1.5–5.2)
D9: 76.7–85.6 (40,732)	31 (0.76)	2.2 (1.2–4.1)	2.1 (1.1–4.1)
D10: > 85.6 (40,613)	44 (1.1)	3.1 (1.7–5.7)	3.3 (1.7–6.2)

OR, odds ratio; CI, confidence interval; Q, quartile; D, decile.

* Isolated anencephalus or spina bifida.

† Adjusted for maternal age, ethnicity, presence of pregestational diabetes mellitus, and year of screening.

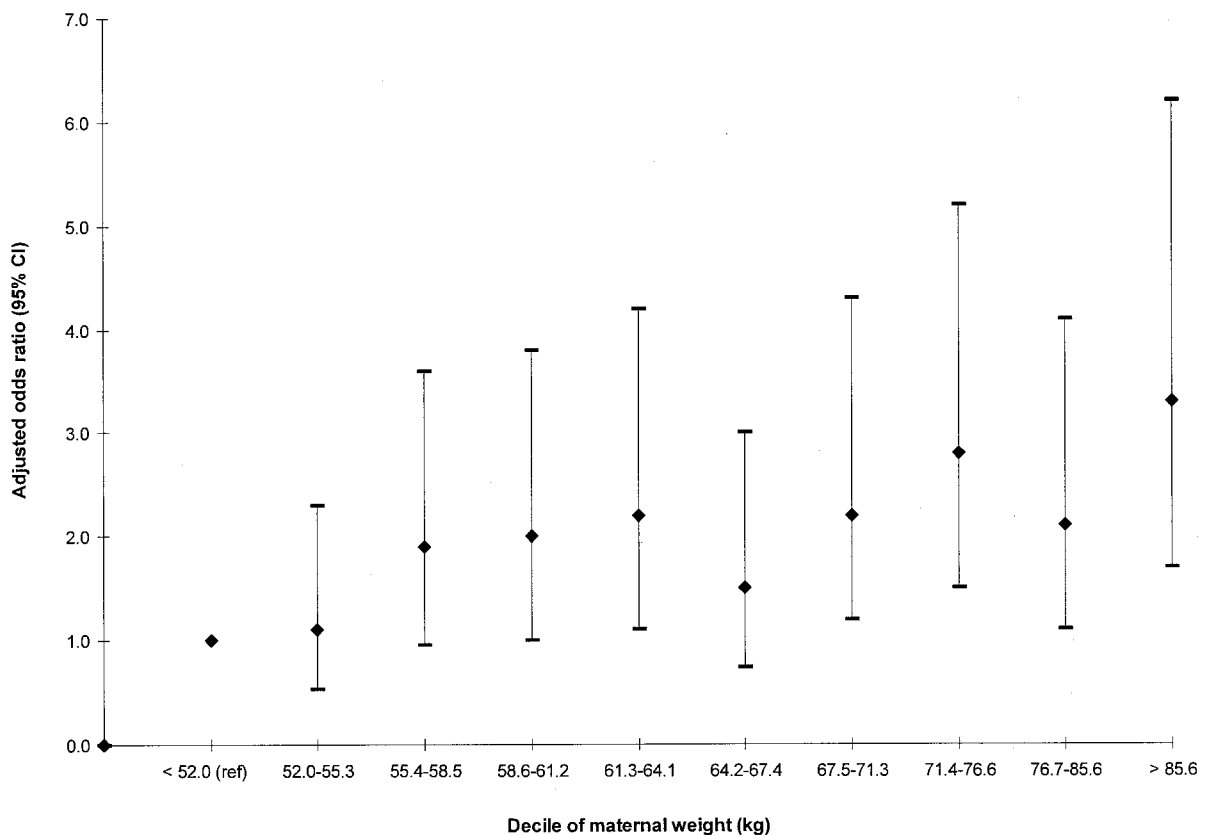


Fig. 1. Associated risk of open neural tube defect according to maternal weight; trend $P < .001$. Adjusted odds ratios (diamonds) and 95% confidence intervals (CIs) (vertical lines).

Ray. Maternal Weight and Neural Tube Defects. *Obstet Gynecol* 2005.



Table 3. Risk of Open Neural Tube Defects in Relation to Elevated Maternal Weight and Folic Acid Flour Fortification

Maternal Weight by Quartile, kg	Adjusted OR* (95% CI)	
	Prefortification (n = 316,064)	Postfortification (n = 90,127)
Q1–Q3: ≤ 73.6	1.0 (ref)	1.0 (ref)
Q4: > 73.6	1.4 (1.0–1.8)	2.8 (1.2–6.6)

OR, odds ratio; CI, confidence interval; Q, quartile.

* Adjusted for maternal age, ethnicity, and presence of pregestational diabetes mellitus.

(Table 3). Moreover, when stratified by weight, women in Q4 had a smaller associated reduction in the relative odds of NTD (44%) than women in Q1 (68%), Q2 (70%) or Q3 (90%) (Table 4).

DISCUSSION

We observed a higher risk of NTD associated with increased maternal weight among women who underwent maternal screening. Despite the introduction of folic acid flour fortification, women of increased weight have remained at significantly higher risk of NTD compared with those in lower weight categories.

Our study is limited by absence of information on folic acid tablet supplementation, and we could only approximate the point at which folic acid flour fortification became clinically significant.^{11–13} We were also unaware of who may have dieted periconceptionally, in an effort to lose weight, thus restricting their folic acid intake; it is possible that this practice was more common among overweight women. Similarly, obese women tend to consume fewer folate-containing fruits and vegetables.¹⁶

Use of self-reported weight has been validated in previous epidemiologic studies,¹⁷ with small variations between self-reported and measured weight in pregnancy.^{18,19} Although we did not measure height, maternal

Table 4. Risk of Open Neural Tube Defects Before and After Folic Acid Flour Fortification, Stratified by Maternal Weight

Maternal weight by quartile, kg (n)	Odds Ratio (95% Confidence Interval)*	
	Crude	Adjusted†
Q1: < 57.1 (101,560)	0.32 (0.098–1.0)	0.36 (0.11–1.2)
Q2: 57.1–64.1 (101,513)	0.30 (0.13–0.68)	0.32 (0.14–0.73)
Q3: 64.2–73.5 (102,040)	0.10 (0.025–0.43)	0.10 (0.025–0.41)
Q4: > 73.6 (101,078)	0.56 (0.31–0.98)	0.52 (0.28–0.96)

Q, quartile.

* Compares postfortification and prefortification rates of open neural tube defects.

† Adjusted for maternal age, ethnicity, and presence of pregestational diabetes mellitus.

weight seems to approximate body mass index (BMI) quite well (correlation coefficient 0.85–0.90).^{20,21} Maternal weight measured at 15 to 20 weeks of gestation also likely provides only an approximation of prepregnancy weight. In this study, maternal weight was estimated at about the same gestational age in all participants, thereby minimizing variability. Second trimester BMI has been shown to be highly correlated with prepregnancy BMI²²; nonetheless, because there is an inverse relationship between prepregnancy BMI and weight gain in the first and second trimesters of pregnancy,²³ we may have underestimated the true relationship between maternal weight and the risk of abnormal closure of the neural tube at 22 to 28 days postconception.

The observed association between maternal obesity and NTD is in keeping with other studies.^{1–3} Although we did not obtain information on maternal dietary patterns, others have found greater caloric intake to be a risk factor for NTD.⁴ In a Californian population-based case-control study of the mothers of 454 NTD-affected fetuses and 462 unaffected controls, the risk of NTD was highest among women whose average dietary glycemic index was in the upper compared with lower quartile (adjusted OR 1.9, 95% CI 1.3–2.7).⁴ This was especially pronounced in those women whose periconceptional BMI was greater than 29 kg/m² (adjusted OR 4.0, 95% CI 1.0–15.7). In addition to dietary intake, maternal inactivity too has been associated with higher NTD risk.⁵ This is especially concerning, given current rates of obesity of 6%, 11%, and 15% among North American women aged 12–19 years, 20–29 years, and 30–39 years, respectively.²⁴ The corresponding rates of sedentary lifestyle, defined as a Physical Activity Index below 1.5 kcal/(kg · d), are 39%, 53%, and 58%.²⁴ Thus, in addition to the other recognized adverse effects of obesity on a woman's health both during^{25,26} and after²⁷ pregnancy, is the ongoing higher risk of NTDs.

These novel data emphasize the ongoing need to encourage proper intake of folic acid periconceptionally, especially among women who are overweight. Whether these women require greater amounts of folic acid remains unknown. Consideration should also be given to the study of prepregnancy weight reduction as a means of preventing NTDs. The simplest and most pragmatic approach might be to promote lower energy intake⁷ and greater energy expenditure (ie, exercise),²⁸ starting at an early age.²⁹

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