High glycemic index diet as a risk factor for depression: analyses from the Women's Health Initiative[1]

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ABSTRACT

Background: The consumption of sweetened beverages, refined foods, and pastries has been shown to be associated with an increased risk of depression in longitudinal studies. However, any influence that refined carbohydrates has on mood could be commensurate with their proportion in the overall diet; studies are therefore needed that measure overall intakes of carbohydrate and sugar, glycemic index (GI), and glycemic load.

Objective: We hypothesized that higher dietary GI and glycemic load would be associated with greater odds of the prevalence and incidence of depression.

Design: This was a prospective cohort study to investigate the relations between dietary GI, glycemic load, and other carbohydrate measures (added sugars, total sugars, glucose, sucrose, lactose, fructose, starch, carbohydrate) and depression in postmenopausal women who participated in the Women's Health Initiative Observational Study at baseline between 1994 and 1998 (n = 87,618) and at the 3-y follow-up (n = 69,954).

Results: We found a progressively higher dietary GI to be associated with increasing odds of incident depression in fully adjusted models (OR for the fifth compared with first quintile: 1.22; 95% CI: 1.09, 1.37), with the trend being statistically significant (P = 0.0032). Progressively higher consumption of dietary added sugars was also associated with increasing odds of incident depression (OR for the fifth compared with first quintile: 1.23; 95% CI: 1.07, 1.41; P-trend = 0.0029). Higher consumption of lactose, fiber, nonjuice fruit, and vegetables was significantly associated with lower odds of incident depression, and nonwhole/refined grain consumption was associated with increased odds of depression.

Conclusions: The results from this study suggest that high-GI diets could be a risk factor for depression in postmenopausal women. Randomized trials should be undertaken to examine the question of whether diets rich in low-GI foods could serve as treatments and primary preventive measures for depression in postmenopausal women. The Women's Health Initiative was registered at clinicaltrials.gov as NCT00000611.   *Am J Clin Nutr* 2015;102:454–63.

Keywords: depression, epidemiology, glycemic index, glycemic load, postmenopausal women

INTRODUCTION

For millions of years our hunter-gatherer ancestors consumed carbohydrates from whole, natural, seasonal, and indigenous fruit and vegetables (1). Because these sources of carbohydrates were nutritious and increased fitness, humans evolved a strong appetite for sweet-tasting foods (2). Our sweet tooth has not served us well, though, since modern technology has provided us with highly refined carbohydrates that are appetizing, inexpensive, and plentiful. It is easy to see how indulging in these foods could increase the risks of obesity and diabetes (3), but it is less clear how doing so could increase the risk of another of our modern scourges, depression.

The WHO predicted that depression will be the second-leading cause of burden on society among all diseases worldwide by the year 2020 (4). Also steadily increasing is the average dietary glycemic index (GI)[9] in the United States (5), with the global consumption of refined foods also increasing as more regions of the world adopt westernized dietary patterns. There is compelling evidence that these 2 trends may intertwine (6–14).

Depression has been found to be associated in cross-sectional studies with the consumption of sweet foods among middle-aged women (6), of ready-made and snack foods among college students (7), and of high-GI foods among homebound elderly individuals (8). However, the relation between depression and carbohydrate consumption is likely to be bidirectional, so associations in cross-sectional studies do not provide evidence of causality. A number of experimental studies found random assignment to diets with a higher glycemic load and carbohydrate

content to have negative effects on mood (9–11), but a limitation of these studies is their small sample sizes. Longitudinal epidemiologic studies have larger sample sizes that allow control of more factors. The consumption of sweetened beverages (12), processed foods (defined as including sweetened desserts, refined grains, fried foods, processed meats, and high-fat dairy products) (13), and processed pastries (muffins, doughnuts, croissants, and other commercial baked goods) (14) has been shown to be associated with an increased risk of depression in longitudinal studies. However, any influence that refined carbohydrates has on mood is likely commensurate with the proportion they constitute in the overall diet, so a limitation of these studies is that they examined only specific types of refined foods, as opposed to dietary GI and glycemic load in the overall diet.

We are aware of only one previous longitudinal epidemiologic study that examined the relation between GI and glycemic load and subsequent depression. That study in 865 Japanese pregnant women found no relation between dietary GI or dietary glycemic load during pregnancy and postpartum depression 2–9 mo after giving birth (15). We tested the hypothesis that higher dietary GI and glycemic load associate with greater odds of prevalent and incident depression in a large, well-characterized sample of postmenopausal women who were followed longitudinally.

METHODS

The Women's Health Initiative (WHI) Observational Study recruited a socioeconomically and racially/ethnically diverse cohort of 93,676 postmenopausal women between the ages of 50 and 79 y from 40 clinical centers in 24 states and the District of Columbia between 1 September 1994 and 31 December 1998 (16). Women were excluded if they did not plan on residing in the area for at least 3 y, had a life expectancy of <3 y, or suffered from substance abuse, mental illness, or dementia. The cross-sectional analyses for this study included women who completed the food questionnaire and the Burnam 8-item scale for depressive disorders at baseline (n = 87,618). Persons with depression at baseline were excluded from the longitudinal analyses, which included women who completed the food questionnaire at baseline and the Burnam 8-item scale for depressive disorders after 3 y of follow-up (n = 69,954). All participants provided informed consent with materials approved by institutional review boards at each center. This study was approved by the institutional review board at Columbia University/New York State Psychiatric Institute.

Ascertainment of dietary variables

Participants completed a 145-item food-frequency questionnaire (FFQ) designed for the WHI at baseline. The dietary variables were computed from average daily intakes of foods and beverages reported on the WHI FFQ. Data were used to test the reliability and validity of the WHI FFQ from 113 women screened for participation in the WHI (17). A mean energy-adjusted correlation coefficient of 0.5 was found between 30 nutrient estimates from the FFQ and the means from four 24-h dietary recalls and a 4-d food record. The energy-adjusted correlation coefficients between carbohydrate and fiber intakes estimated by the WHI FFQ and 8 d of dietary intake were 0.63 and 0.65, respectively. The test-retest reliability of the nutrient intake

estimates between the first and second administration of the questionnaire was high. The GI is defined as an index of the postprandial glucose response of a food, compared with an equal amount of carbohydrate (typically 50 g) from a reference food, usually glucose or white bread (18, 19). The GI variable in the WHI was applied to available carbohydrate (total carbohydrate less fiber), and glucose was used as the reference food. The GI of a specific food is equal to the blood glucose incremental AUC of the test food for a given time postconsumption divided by the blood glucose incremental AUC of the reference food multiplied by 100. Dietary GI is considered as a quality of carbohydrate-based foods in the overall diet and is estimated as the weighted average (with weights based on the total carbohydrate content per serving consumed) of the GI values of all carbohydrate foods consumed during the dietary period. Glycemic load is equal to the GI of an individual food multiplied by the total grams of carbohydrate per serving divided by 100. Dietary glycemic load is estimated as the sum of the glycemic loads of all carbohydrate goods consumed during the dietary period. For this study, glycemic load is based on the grams of carbohydrates consumed per day. The methodology used to construct the GI and glycemic load database for the WHI is described in detail elsewhere (18).

Although our primary exposures of interest were GI and glycemic load as risk factors for depression, we also investigated other measures of carbohydrate consumption computed from average daily intakes of foods and beverages reported on the WHI FFQ, including dietary added sugar, total sugars, specific types of sugars (glucose, sucrose, lactose, fructose), starch, and total carbohydrate. Added sugars were assessed according to the MyPyramid Equivalents 2.0 and included all sugars used as ingredients in processed and prepared foods such as breads, cakes, sodas, jellies, chocolates, and ice cream and sugars consumed separately or added to foods at the table (20). Total carbohydrate was calculated by difference rather than analyzed directly. In post hoc analyses we examined the association between the consumption of dietary fiber and specific foods (whole grains, nonwhole/refined grains, nonjuice fruits, vegetables, nuts/seeds, and legumes) and the incidence of depression. Dietary fiber and specific types and sources of carbohydrates were categorized into quintiles for analyses.

Ascertainment of depression

Depressive symptoms were measured by using participant responses to the Burnam 8-item scale for depressive disorders administered at baseline and at the 3-y follow-up. The Burnam scale includes 2 items from the Diagnostic Interview Schedule and 6 items from the Center for Epidemiologic Studies–Depression Scale. Questionnaire responses were used to calculate the Burnam score with the use of a logistic regression–based algorithm; values for the scale ranged from 0 to 99, with higher scores indicating greater depressive symptomatology. A standard threshold of 0.06 was used to identify women who experienced symptoms consistent with depressive disorders such as major depression and dysthymia (21).

Covariates

Covariates in the analyses included the following: age (5-y interval), race-ethnicity (American Indian, Asian/Pacific Islander,

black, Hispanic, white not of Hispanic origin, unknown, or missing), education (less than high school graduate, high school graduate, some college, college graduate, postgraduate, or missing), annual income (<$10,000, $10,000–19,999, $20,000–34,999, $35,000–49,999, $50,000–74,999, $75,000–99,999, $100,000–149,999, ≥$150,000, don't know, or missing), BMI (in kg/m²; underweight, <18.5; normal, 18.5–24.9; overweight, 25.0–29.9; obesity I, 30.0–34.9; obesity II, 35.0–39.9; obesity III, ≥40; or missing), diabetes (no, yes, or missing), hypertension (no, yes, or missing), myocardial infarction (no, yes, or missing), stroke (no, yes, or missing), cardiovascular disease (no, yes, or missing), cancer (no, yes, or missing), Alzheimer disease (no, yes, or missing), hormone replacement therapy (no, yes, or missing), physical activity [in metabolic equivalents (METs); <3, 3 to <9, 9 to <18, 18 to <27, or ≥27 MET-h/wk (1 MET = 58.2 W/m²) or missing], alcohol intake (nondrinker, past drinker, <1 drink/mo, <1 drink/wk, 1 to <7 drinks/wk, ≥7 drinks/wk, or missing), smoking status (never smoked, past smoker, current smoker, or missing), stressful life events (in quintiles or missing), social support (in quintiles or missing), and energy-adjusted intakes of SFAs (continuous), MUFAs (continuous), PUFAs (continuous), *trans* fat (continuous), dietary fiber (continuous), fruit (continuous), vegetables (continuous), legumes (continuous), nuts/seeds (continuous), dietary fiber (continuous), and Healthy Eating Index score (continuous).

Statistical analyses

Chi-square tests for categorical variables and *t* tests for continuous variables were used to explore differences by depression and by GI quintiles. Multivariable logistic regression was used to calculate ORs to examine the cross-sectional relation between dietary GI and glycemic load and the prevalence of depression. Persons with depression were excluded from the longitudinal analyses. The longitudinal relation between dietary variables and incident depression 3 y later was examined by using multivariable logistic regression to calculate ORs adjusted using the energy partition (22) (model 1). Covariates in the first multivariate-adjusted model (model 2) included age, race-ethnicity, education, income, BMI, diabetes, hypertension, myocardial infarction, stroke, cardiovascular disease, cancer, Alzheimer disease, hormone replacement therapy, physical activity, alcohol, smoking, stressful life events, social support, and energy-adjusted intakes of SFAs, MUFAs, PUFAs, and *trans* fatty acids. The final adjusted model (model 3) included the variables in model 2 plus covariates that directly affect average GI, including energy-adjusted intakes of fruit, vegetables, legumes, nuts/seeds, fiber, and Healthy Eating Index score. Tests for linear trend were performed by modeling a numeric value (−2, −1, 0, 1, 2) for each dietary quintile category. The 95% confidence limits for ORs were used to determine the significance of individual coefficients in the logistic regression models. We controlled for a false discovery rate of 0.15 using the Benjamini-Hochberg procedure in post hoc analyses where we examined the association between the consumption of dietary fiber and specific foods (whole grains, nonwhole/refined grains, nonjuice fruit, vegetables, nuts/seeds, and legumes) and depression incidence (23). All statistical analyses were conducted by using SAS statistical software version 9.1 (SAS Institute).

RESULTS

Baseline characteristics for women in the WHI Observational Study population according to their GI quintile based on available carbohydrate and incidence of depression 3 y later are shown in **Tables 1** and **2**. Higher GI quintiles were associated with younger age; higher BMI; less physical activity; higher intakes of non–energy-adjusted SFAs, MUFAs, PUFAs, and *trans* fat; and lower intakes of fruit, vegetables, legumes, nuts/seeds, dietary fiber, and Healthy Eating Index score. Higher GI quintiles were also associated with black race-ethnicity, lower education, lower income, hypertension, myocardial infarction, less hormone replacement therapy, smoking, more stressful life events, and less social support. Depression was associated with higher GI quintiles; younger age; higher BMI; less physical activity; higher intakes of SFAs, MUFAs, PUFAs, and *trans* fat; and lower intakes of fruit, vegetables, dietary fiber, and Healthy Eating Index score. Depression was also associated with Hispanic race-ethnicity, lower education, lower income, diabetes, hypertension, stroke, cardiovascular disease, cancer, Alzheimer disease, higher hormone replacement therapy, smoking, more stressful life events, and less social support.

Table 3 shows the results from the cross-sectional multivariable analyses. In energy-adjusted results (model 1), participants whose dietary GIs according to available carbohydrate were in the third, fourth, and fifth quintiles were significantly more likely to have depression than were participants who were in the first quintile. The relation between depression and glycemic load was U-shaped in energy-adjusted results (model 1), with participants whose dietary glycemic loads were in the second, third, and fourth quintiles being significantly less likely to have depression than participants in the first quintile. The inclusion of the variables in model 2 attenuated the associations, with the result that only the fifth quintile for both GI and glycemic load was significantly associated with depression. The inclusion of the covariates that directly affect average GI in model 3 further attenuated the results, with the fifth quintile no longer being significant. Tests for trend were significant for models 1 and 2 for GI but not for model 3 or any of the glycemic load models.

The results from the longitudinal multivariable analyses for GI and glycemic load on the basis of available carbohydrate are shown in **Table 4**. Participants whose dietary GIs were in the fourth and fifth quintiles were significantly more likely to have depression 3 y later than were participants who were in the first quintile in energy-adjusted results (model 1). Results were attenuated with the inclusion of the variables in model 2 and further so with the inclusion of covariates that directly affect average GI in model 3, yet participants in the fourth and fifth quintiles for dietary GI remained significantly more likely to have depression 3 y later in fully adjusted multivariable models. Tests for trend for dietary GI were significant in each of the longitudinal models. No association between glycemic load and depression incidence was found.

Table 5 shows the results from the longitudinal multivariable analyses for the other measures of energy-adjusted carbohydrate consumption. As the consumption of dietary added sugars increased, the likelihood of experiencing depression 3 y later increased, with the trend being significant. Participants in the fourth and fifth quintiles for dietary added sugars were significantly more likely to have incident depression in each of the

TABLE 1
Baseline characteristics by dietary GI quintile and incidence of depression 3 y later[1]

Baseline characteristics	Dietary GI quintile						Incident depression 3 y later		
	First (low)	Second	Third	Fourth	Fifth (high)	P^2	Yes	No	P^2
Burnam score	0.0209 ± 0.09	0.0201 ± 0.08	0.0215 ± 0.09	0.0233 ± 0.09	0.0273 ± 0.10	<0.0001	0.2745 ± 0.23	0.0047 ± 0.01	<0.0001
Age, y	64.2 ± 7.3	64.0 ± 7.3	63.9 ± 7.3	63.6 ± 7.2	63.0 ± 7.2	<0.0001	62.7 ± 7.5	63.8 ± 7.2	<0.0001
BMI, kg/m²	26.4 ± 5.3	26.5 ± 5.4	26.8 ± 5.5	27.2 ± 5.7	27.9 ± 6.1	<0.0001	28.0 ± 6.1	26.9 ± 5.6	<0.0001
Physical activity, MET-h/wk	17.7 ± 16.0	15.9 ± 14.7	14.4 ± 14.1	13.1 ± 13.6	10.9 ± 12.8	<0.0001	12.3 ± 13.7	14.5 ± 14.5	<0.0001
SFAs, g	14.9 ± 8.9	16.7 ± 9.4	17.8 ± 10.0	19.1 ± 11.1	20.1 ± 11.5	<0.0001	19.4 ± 11.7	17.6 ± 10.3	<0.0001
MUFAs, g	16.7 ± 9.3	18.9 ± 10.0	20.2 ± 10.7	21.6 ± 11.8	23.0 ± 12.5	<0.0001	21.9 ± 12.5	19.9 ± 11.0	<0.0001
PUFAs, g	9.5 ± 5.2	10.5 ± 5.4	11.1 ± 5.9	11.9 ± 6.4	12.5 ± 7.0	<0.0001	12.0 ± 6.9	11.0 ± 6.0	<0.0001
trans Fat, g	2.6 ± 1.9	3.2 ± 2.2	3.6 ± 2.5	4.1 ± 2.8	4.8 ± 3.2	<0.0001	4.0 ± 3.0	3.7 ± 2.6	<0.0001
Fruit, medium portion	2.4 ± 1.4	2.4 ± 1.3	2.2 ± 1.2	1.9 ± 1.2	1.5 ± 1.1	<0.0001	2.0 ± 1.3	2.1 ± 1.3	<0.0001
Vegetables, medium portion	3.0 ± 1.5	2.6 ± 1.3	2.4 ± 1.2	2.1 ± 1.2	1.7 ± 1.1	<0.0001	2.2 ± 1.4	2.4 ± 1.3	<0.0001
Legumes, cups	0.10 ± 0.1	0.11 ± 0.1	0.10 ± 0.1	0.09 ± 0.1	0.06 ± 0.1	<0.0001	0.09 ± 0.1	0.09 ± 0.1	0.0164
Nuts/seeds, oz	0.38 ± 0.6	0.36 ± 0.6	0.35 ± 0.5	0.34 ± 0.5	0.30 ± 0.5	<0.0001	0.35 ± 0.6	0.35 ± 0.5	0.4737
Dietary fiber, g	16.8 ± 6.9	17.7 ± 7.0	17.4 ± 7.0	16.7 ± 6.9	15.0 ± 6.5	<0.0001	16.5 ± 7.1	16.7 ± 6.9	0.0157
Healthy Eating Index score	72.9 ± 9.3	72.7 ± 9.0	71.2 ± 9.3	68.8 ± 9.8	63.7 ± 10.8	<0.0001	68.0 ± 10.7	70.0 ± 10.2	<0.0001

[1] All values are means ± SDs. GI, glycemic index; MET, metabolic equivalent; oz, ounces (1 oz = 28.3495 g).

[2] Differences by depression and GI quintiles were tested by using *t* tests for continuous variables.

models. Increasing consumption of sucrose was associated with an increased risk of depression incidence in results from model 2, with participants in the fifth quintile being significantly more likely to experience depression 3 y later, and with the trend being significant. The association of sucrose and depression incidence became nonsignificant with the inclusion in model 3 of variables that include carbohydrates and affect their absorption. The odds of the incidence of depression decreased with higher amounts of dietary lactose consumption, and the trends were significant. Participants in the fifth quintile of lactose consumption were significantly less likely to have incident depression in the fully adjusted model. We found no relation between depression incidence and dietary total sugar, glucose, fructose, starch, or total carbohydrate.

The results from our post hoc analyses exploring the associations between energy-adjusted dietary fiber, specific foods, and incident depression are shown in **Table 6**. Increased consumption of dietary fiber was associated with decreased ORs for depression. Progressively increasing consumption of whole grains was associated with lower depression incidence, but these relations became nonsignificant in the fully adjusted model. A higher consumption of nonwhole/refined grains was associated with higher incidence of depression, with participants in the fifth quintile being significantly more likely to have depression incidence. As consumption of fruit and vegetables increased, the odds of depression incidence 3 y later decreased, with the trends being significant. Participants in the third, fourth, and fifth quintiles for nonjuice fruit and for vegetables were significantly less likely to have depression incidence in fully adjusted models. The fifth quintiles for fiber, non–whole grains, fruit, and vegetables continued to be significant after the false discovery rate of 0.15 was controlled for by using the Benjamini-Hochberg procedure. The consumption of nuts/seeds and legumes was not associated with the incidence of depression.

DISCUSSION

We found a progressively higher dietary GI to be associated with increasing odds of depression incidence in carefully controlled analyses. We found added sugars, but not total sugars or total carbohydrates, to be strongly associated with depression incidence. This could be attributed to added sugars, caloric sweeteners not naturally found in foods, having higher GIs on average. Dietary total sugars comprise an amalgam of various types of sugar and sugar from different food sources. In our analyses, the fifth quintile of glucose, a high-GI sugar, and sucrose, an intermediate-GI sugar, showed elevated although nonsignificant ORs for depression incidence in fully adjusted models. However, increased consumption of lactose, a low-GI sugar, was associated with significantly lower odds for depression incidence. The food source of sugar influences the GI, with higher fiber content slowing the metabolism of carbohydrate and lowering the GI. Our finding that higher dietary fiber content was associated with lower odds of depression could be due to its influence on GI. We also found that the increased consumption of vegetables and nonjuice fruit was associated with lower odds for depression. Although the GIs of fruit vary, of the 7 most commonly consumed fruit in the United States, 4 have low GIs (apples, strawberries, oranges, and peaches), 2 have intermediate GIs (ripe bananas and grapes), and only one has a high GI (watermelon) (24). A relatively low GI could be one of the attributes of fruit that contributes toward their association with lower odds for depression.

In the present analysis, no relation was found between dietary starch and depression incidence. Starches are complex carbohydrates, but some sources, such as refined white bread and boiled potatoes, have a high GI, whereas others that are rich in fiber, such as legumes, nuts/seeds, and yams, have a low GI. We found that progressively higher consumption of whole grains was associated with lower odds for depression incidence, whereas the

TABLE 2
Baseline characteristics by dietary GI quintile and incidence of depression 3 y later[1]

Baseline characteristics	n	Dietary GI quintile						Incident depression 3 y later		
		First (low)	Second	Third	Fourth	Fifth (high)	P[2]	Yes	No	P[2]
Total n	69,954	13,990	13,991	13,991	13,991	13,991		4643	65,311	
Depression, n	4643	807	849	876	988	1123	<0.0001			
Median GI		47.0	49.8	51.7	53.5	56.3				
Race-ethnicity, %							<0.0001			<0.0001
American Indian/Alaskan native	928	1.4	1.3	1.2	1.2	1.5		8.2	91.8	
Asian/Pacific Islander	2061	2.5	3.3	3.3	3.5	2.2		3.7	96.3	
Black	4328	4.8	4.0	5.1	6.5	10.7		8.1	91.9	
Hispanic	1879	3.3	2.7	2.5	2.7	2.3		11.2	88.8	
White, not of Hispanic origin	60,570	87.7	88.4	87.8	85.9	83.1		6.5	93.5	
Missing	188	0.3	0.3	0.2	0.3	0.3		5.9	94.1	
Education (college graduate or higher), %	31,285	52.0	49.8	46.3	41.9	33.6	<0.0001	36.7	45.3	<0.0001
Annual income ≥$50,000, %	28,309	47.1	45.2	42.9	40.5	35.6	<0.0001	35.3	42.7	<0.0001
Diabetes, %	3217	4.6	4.3	4.5	4.7	4.9	0.2470	6.8	4.4	<0.0001
Hypertension, %	21,958	29.1	29.9	31.4	32.5	34.1	<0.0001	34.4	31.2	<0.0001
Myocardial infarction, %	1458	1.9	1.8	1.9	2.3	2.4	0.0007	2.4	2.1	0.1738
Stroke, %	821	1.1	1.0	1.1	1.3	1.4	0.0562	1.8	1.1	<0.0001
Cardiovascular disease, %	12,436	17.2	17.8	18.1	17.7	18.1	0.0943	21.3	17.5	<0.0001
Cancer, %	8804	12.5	12.8	13.1	12.4	12.1	0.1740	14.1	12.5	0.0008
Alzheimer disease	32	0.05	0.04	0.06	0.05	0.03	0.7050	0.09	0.04	0.0002
Hormone replacement therapy, %	34,193	50.8	50.7	49.2	48.3	45.5	<0.0001	49.8	48.8	0.0002
Alcohol intake, %							<0.0001			<0.0001
Nondrinker	7220	8.4	8.6	9.6	11.0	14.0		6.6	93.4	
Past drinker	11,767	15.1	14.7	15.8	17.6	20.9		8.6	91.4	
<1 drink/mo	7860	9.4	9.9	10.8	11.6	14.5		6.8	93.2	
<1 drink/wk	14,043	19.0	20.3	20.5	21.0	19.6		6.7	93.3	
1 to <7 drinks/wk	19,047	28.7	30.6	29.1	26.7	21.2		5.8	94.2	
≥7 drinks/wk	9642	18.7	15.6	13.7	11.7	9.2		5.4	94.6	
Missing	376	0.7	0.5	0.5	0.5	0.6		8.2	91.8	
Smoking status, %							<0.0001			<0.0001
Never smoked	35,617	48.6	51.6	51.4	51.8	51.2		6.2	93.8	
Past smoker	29,869	45.9	43.3	42.4	41.5	40.4		6.7	93.3	
Current smoker	3581	4.1	3.9	4.9	5.5	7.2		9.9	90.1	
Missing	888	1.4	1.2	1.3	1.2	1.2		7.3	92.7	
Stressful life events, %							<0.0001			<0.0001
First quintile	20,107	29.3	29.7	29.4	28.4	27.0		2.4	97.6	
Second quintile	8930	12.6	13.1	13.1	12.8	12.3		2.8	97.2	
Third quintile	11,838	16.7	17.1	17.2	17.2	16.4		3.9	96.1	
Fourth quintile	15,604	22.1	22.3	22.0	22.2	23.0		7.6	92.4	
Fifth quintile	12,317	17.5	16.2	16.7	17.8	19.3		17.6	82.4	
Missing	1159	1.8	1.6	1.7	1.7	1.6		9.6	90.4	
Social support, %							<0.0001			<0.0001
First quintile	14,317	20.2	19.5	20.3	20.5	21.9		10.4	89.6	
Second quintile	14,632	21.0	20.7	20.8	21.3	20.8		7.4	92.7	
Third quintile	10,506	14.4	15.3	15.2	15.4	14.8		5.6	94.4	
Fourth quintile	13,700	19.1	20.2	19.4	19.7	19.4		5.3	94.7	
Fifth quintile	15,201	22.8	22.2	22.2	20.8	20.7		4.2	95.9	
Missing	1599	2.4	2.2	2.2	2.3	2.4		7.8	92.3	

[1] GI, glycemic index.
[2] Differences by depression and GI quintiles were tested by using chi-square tests for categorical variables.

opposite was true for nonwhole/refined grains, with progressively higher consumption associated with higher odds for depression. In our analysis, increased vegetable consumption was associated with decreased odds for depression. Any attempt to relate GI to the influence of vegetable consumption on depression is thwarted by the fact that the most commonly consumed vegetable by far in the United States is potatoes (25), with most varieties and methods of cooking resulting in a high GI (26), whereas the next 6 most commonly consumed vegetables (tomatoes, onions, head lettuce, sweet corn, romaine and leaf lettuce, and chili peppers) all have low GIs (25). We found no significant relation between depression incidence and nuts/seeds or legumes, but this could be attributed to these foods accounting for small proportions of the overall diet.

Our results could be viewed as being somewhat counterintuitive because depressed individuals are often presumed to consume carbohydrates to self-medicate their depression. The

TABLE 3
Adjusted ORs (95% CIs) from logistic regression analyses of depression prevalence according to quintiles of energy partition–adjusted GI and glycemic load[1]

	Median	Prevalent depression at baseline, n	Prevalent depression at baseline, OR (95% CI)		
			Model 1	Model 2	Model 3
Dietary GI					
First quintile	47.1	1667	1.00	1.00	1.00
Second quintile	49.9	1710	1.04 (0.97, 1.12)	1.04 (0.96, 1.12)	1.02 (0.95, 1.10)
Third quintile	51.8	1914	1.10 (1.02, 1.18)	1.05 (0.97, 1.13)	1.02 (0.95, 1.10)
Fourth quintile	53.7	1997	1.16 (1.08, 1.24)	1.02 (0.95, 1.10)	0.98 (0.91, 1.06)
Fifth quintile	56.5	2504	1.51 (1.42, 1.62)	1.16 (1.07, 1.25)	1.08 (0.99, 1.17)
P-trend			<0.0001	0.0004	0.2420
Dietary glycemic load, g/d					
First quintile	57.9	1992	1.00	1.00	1.00
Second quintile	80.8	1783	0.86 (0.80, 0.92)	0.97 (0.90, 1.05)	0.94 (0.86, 1.02)
Third quintile	99.7	1739	0.80 (0.75, 0.86)	0.94 (0.86, 1.03)	0.89 (0.80, 0.99)
Fourth quintile	121.2	1867	0.84 (0.78, 0.90)	1.00 (0.90, 1.11)	0.93 (0.83, 1.05)
Fifth quintile	159.8	2411	1.05 (0.97, 1.13)	1.16 (1.01, 1.32)	1.05 (0.90, 1.22)
P-trend			0.7789	0.0598	0.3951

[1]Model 1 was energy partition adjusted; model 2 adjusted for variables in model 1 plus age, race-ethnicity, education, income, BMI, diabetes, hypertension, myocardial infarction, stroke, cardiovascular disease, cancer, Alzheimer disease, hormone replacement therapy, physical activity, alcohol, smoking, stressful life events, social support, and energy-adjusted intakes of SFAs, MUFAs, PUFAs, and *trans* fatty acids; model 3 adjusted for variables in model 2 plus energy-adjusted intakes of fruit, vegetables, legumes, nuts/seeds, and fiber and Healthy Eating Index score. GI, glycemic index.

pleasure of eating sweet foods could give temporary solace to those who are depressed. Carbohydrate intake has also been theorized to facilitate the synthesis of serotonin in the brain (27). Tryptophan, a precursor of serotonin, competes with larger amino acids for the same transport system to cross the blood-brain barrier (28). Insulin released after carbohydrate intake stimulates the uptake of the competing larger amino acids into muscle tissue, increasing the ratio of tryptophan to the other amino acids in plasma, which allows tryptophan access to the transport system to cross the blood-brain barrier and to contribute toward serotonin synthesis (29). However, for this process to occur, the meal must be made up entirely of carbohydrate and consumed without any protein remaining in the gut. If the meal contains as little as 2.5% protein, the increase in tryptophan will be blunted; and if the meal contains as little as 5% protein, then tryptophan concentrations will not increase (30). Sweet foods such as ice cream, milk chocolate, sweetened yogurts, and egg-based cakes and pastries contain enough protein to block any increase in tryptophan. Even

TABLE 4
Adjusted ORs (95% CIs) from logistic regression analyses of depression incidence according to quintiles of energy partition–adjusted GI and glycemic load[1]

	Median	Incident depression after 3 y, n	Incident depression 3 y later, OR (95% CI)		
			Model 1	Model 2	Model 3
Dietary GI					
First quintile	47.0	807	1.00	1.00	1.00
Second quintile	49.8	849	1.06 (0.96, 1.17)	1.10 (0.99, 1.22)	1.10 (0.99, 1.22)
Third quintile	51.7	876	1.10 (1.00, 1.21)	1.10 (0.99, 1.22)	1.11 (1.00, 1.23)
Fourth quintile	53.5	988	1.19 (1.08, 1.32)	1.14 (1.03, 1.26)	1.14 (1.03, 1.27)
Fifth quintile	56.3	1123	1.42 (1.29, 1.55)	1.24 (1.12, 1.37)	1.22 (1.09, 1.37)
P-trend			<0.0001	<0.0001	0.0032
Dietary glycemic load, g/d					
First quintile	58.5	911	1.00	1.00	1.00
Second quintile	81.2	907	0.98 (0.89, 1.08)	1.07 (0.96, 1.20)	1.03 (0.92, 1.16)
Third quintile	99.7	848	0.91 (0.82, 1.01)	1.03 (0.91, 1.17)	0.98 (0.85, 1.12)
Fourth quintile	120.7	919	0.94 (0.85, 1.04)	1.08 (0.94, 1.25)	1.01 (0.86, 1.19)
Fifth quintile	157.9	1058	1.02 (0.91, 1.13)	1.09 (0.91, 1.32)	1.01 (0.82, 1.24)
P-trend			0.7455	0.4582	0.9581

[1]Model 1 was energy partition adjusted; model 2 adjusted for variables in model 1 plus age, race-ethnicity, education, income, BMI, diabetes, hypertension, myocardial infarction, stroke, cardiovascular disease, cancer, Alzheimer disease, hormone replacement therapy, physical activity, alcohol, smoking, stressful life events, social support, and energy-adjusted intakes of SFAs, MUFAs, PUFAs, and *trans* fatty acids; model 3 adjusted for variables in model 2 plus energy-adjusted intakes of fruit, vegetables, legumes, nuts/seeds, and fiber and Healthy Eating Index score. GI, glycemic index.

TABLE 5
Adjusted ORs (95% CIs) from logistic regression analyses of depression incidence according to quintiles of specific measures of energy partition–adjusted carbohydrate consumption[1]

	Median, g	Incident depression after 3 y, *n*	Incident depression 3 y later, OR (95% CI)		
			Model 1	Model 2	Model 3
Dietary added sugar					
First quintile	17.8	820	1.00	1.00	1.00
Second quintile	28.8	853	1.07 (0.97, 1.19)	1.09 (0.99, 1.22)	1.08 (0.97, 1.20)
Third quintile	39.3	839	1.07 (0.96, 1.19)	1.09 (0.98, 1.21)	1.06 (0.94, 1.19)
Fourth quintile	52.5	973	1.25 (1.13, 1.39)	1.22 (1.09, 1.36)	1.18 (1.04, 1.33)
Fifth quintile	79.2	1158	1.46 (1.31, 1.63)	1.29 (1.13, 1.46)	1.23 (1.07, 1.41)
P-trend			<0.0001	<0.0001	0.0029
Dietary total sugars					
First quintile	50.7	950	1.00	1.00	1.00
Second quintile	73.9	892	0.91 (0.83, 1.00)	1.00 (0.90, 1.11)	0.99 (0.89, 1.11)
Third quintile	93.3	894	0.89 (0.81, 0.98)	1.04 (0.93, 1.16)	1.02 (0.90, 1.16)
Fourth quintile	115.6	900	0.87 (0.79, 0.96)	1.04 (0.92, 1.18)	1.02 (0.88, 1.17)
Fifth quintile	155.3	1007	0.91 (0.82, 1.01)	1.02 (0.88, 1.19)	0.99 (0.83, 1.18)
P-trend			0.0621	0.6595	0.9926
Dietary glucose					
First quintile	10.2	971	1.00	1.00	1.00
Second quintile	15.6	888	0.89 (0.81, 0.98)	1.04 (0.94, 1.15)	1.07 (0.96, 1.19)
Third quintile	20.1	888	0.87 (0.79, 0.96)	1.05 (0.94, 1.17)	1.09 (0.97, 1.23)
Fourth quintile	25.1	885	0.85 (0.76, 0.93)	1.05 (0.94, 1.18)	1.10 (0.96, 1.26)
Fifth quintile	34.5	1011	0.92 (0.83, 1.01)	1.10 (0.97, 1.25)	1.16 (0.99, 1.36)
P-trend			0.0575	0.1691	0.0822
Dietary sucrose					
First quintile	15.5	903	1.00	1.00	1.00
Second quintile	23.7	870	0.96 (0.87, 1.06)	1.04 (0.94, 1.15)	1.03 (0.93, 1.14)
Third quintile	31.2	893	0.98 (0.89, 1.09)	1.09 (0.98, 1.22)	1.07 (0.96, 1.20)
Fourth quintile	40.2	928	1.00 (0.90, 1.11)	1.12 (1.00, 1.26)	1.09 (0.97, 1.23)
Fifth quintile	57.4	1049	1.05 (0.94, 1.18)	1.16 (1.02, 1.32)	1.12 (0.97, 1.28)
P-trend			0.2863	0.0143	0.0805
Dietary lactose					
First quintile	4.3	999	1.00	1.00	1.00
Second quintile	9.3	931	0.90 (0.82, 0.99)	0.93 (0.85, 1.03)	0.93 (0.84, 1.03)
Third quintile	14.7	928	0.87 (0.79, 0.96)	0.94 (0.85, 1.04)	0.93 (0.84, 1.03)
Fourth quintile	21.6	921	0.84 (0.76, 0.92)	0.91 (0.82, 1.01)	0.90 (0.80, 1.00)
Fifth quintile	38.0	864	0.75 (0.67, 0.83)	0.83 (0.74, 0.94)	0.81 (0.72, 0.92)
P-trend			<0.0001	0.0052	0.0022
Dietary fructose					
First quintile	9.3	1005	1.00	1.00	1.00
Second quintile	14.9	876	0.85 (0.77, 0.93)	0.98 (0.88, 1.08)	1.00 (0.90, 1.11)
Third quintile	19.7	868	0.82 (0.75, 0.91)	0.99 (0.89, 1.10)	1.02 (0.91, 1.14)
Fourth quintile	25.3	907	0.85 (0.77, 0.93)	1.02 (0.92, 1.14)	1.06 (0.93, 1.20)
Fifth quintile	35.4	987	0.88 (0.80, 0.97)	1.01 (0.89, 1.14)	1.04 (0.89, 1.21)
P-trend			0.0270	0.6683	0.4698
Dietary starch					
First quintile	38.4	915	1.00	1.00	1.00
Second quintile	56.1	835	0.91 (0.83, 1.01)	0.96 (0.86, 1.07)	0.94 (0.84, 1.05)
Third quintile	70.7	909	0.99 (0.89, 1.10)	1.07 (0.96, 1.20)	1.05 (0.93, 1.19)
Fourth quintile	88.0	930	0.98 (0.88, 1.09)	1.06 (0.93, 1.20)	1.03 (0.89, 1.18)
Fifth quintile	119.3	1054	1.02 (0.91, 1.15)	1.04 (0.90, 1.21)	1.01 (0.85, 1.20)
P-trend			0.4098	0.3248	0.5912
Dietary total carbohydrate					
First quintile	115.5	931	1.00	1.00	1.00
Second quintile	158.5	903	0.94 (0.86, 1.04)	1.04 (0.93, 1.16)	1.01 (0.89, 1.13)
Third quintile	193.4	853	0.86 (0.78, 0.95)	1.00 (0.88, 1.14)	0.96 (0.83, 1.11)
Fourth quintile	232.8	929	0.91 (0.82, 1.01)	1.06 (0.91, 1.23)	1.01 (0.85, 1.20)
Fifth quintile	301.9	1027	0.93 (0.84, 1.04)	1.02 (0.83, 1.25)	0.97 (0.77, 1.22)
P-trend			0.1615	0.8322	0.8250

[1]Model 1 was energy partition adjusted; model 2 adjusted for variables in model 1 plus age, race-ethnicity, education, income, BMI, diabetes, hypertension, myocardial infarction, stroke, cardiovascular disease, cancer, Alzheimer disease, hormone replacement therapy, physical activity, alcohol, smoking, stressful life events, social support, and energy-adjusted intakes of SFAs, MUFAs, PUFAs, and *trans* fatty acids; model 3 adjusted for variables in model 2 plus energy-adjusted intakes of fruit, vegetables, legumes, nuts/seeds, and fiber and Healthy Eating Index score.

TABLE 6
Adjusted ORs (95% CIs) of incident depression according to quintiles of specific nutrient density–adjusted foods[1]

	Median	Incident depression after 3 y, *n*	Incident depression 3 y later, OR (95% CI)	
			Model 1	Model 2
Fiber, g				
First quintile	10.719	1154	1.00	1.00
Second quintile	13.725	982	0.84 (0.77, 0.92)	0.96 (0.87, 1.06)
Third quintile	16.061	930	0.79 (0.72, 0.87)	0.97 (0.88, 1.08)
Fourth quintile	18.306	817	0.69 (0.63, 0.76)	0.91 (0.81, 1.01)
Fifth quintile	21.136	760	0.64 (0.58, 0.70)	0.86 (0.76, 0.98)
P-trend			<0.0001	0.0188
Whole grains, oz				
First quintile	0.251	1066	1.00	1.00
Second quintile	0.690	1025	0.96 (0.88, 1.05)	1.04 (0.95, 1.15)
Third quintile	1.069	904	0.84 (0.76, 0.92)	0.96 (0.87, 1.06)
Fourth quintile	1.474	836	0.77 (0.70, 0.85)	0.93 (0.84, 1.03)
Fifth quintile	2.293	812	0.75 (0.68, 0.82)	0.92 (0.82, 1.02)
P-trend			<0.0001	0.0166
Nonwhole/refined grains, oz				
First quintile	1.720	858	1.00	1.00
Second quintile	2.627	826	0.96 (0.87, 1.06)	0.94 (0.85, 1.04)
Third quintile	3.277	964	1.13 (1.03, 1.25)	1.07 (0.97, 1.18)
Fourth quintile	3.946	962	1.13 (1.03, 1.24)	1.04 (0.94, 1.15)
Fifth quintile	5.271	1033	1.22 (1.11, 1.34)	1.12 (1.01, 1.24)
P-trend			<0.0001	0.0072
Nonjuice fruit, cups				
First quintile	0.248	1198	1.00	1.00
Second quintile	0.667	954	0.78 (0.71, 0.85)	0.92 (0.84, 1.01)
Third quintile	0.885	876	0.70 (0.64, 0.76)	0.88 (0.80, 0.97)
Fourth quintile	1.647	840	0.65 (0.59, 0.71)	0.88 (0.79, 0.98)
Fifth quintile	2.338	775	0.63 (0.58, 0.70)	0.88 (0.79, 0.99)
P-trend			<0.0001	0.0247
Vegetables, medium portion				
First quintile	0.997	1222	1.00	1.00
Second quintile	1.603	975	0.78 (0.72, 0.85)	0.93 (0.84, 1.02)
Third quintile	2.132	851	0.68 (0.62, 0.74)	0.88 (0.79, 0.97)
Fourth quintile	2.778	803	0.64 (0.58, 0.70)	0.86 (0.78, 0.96)
Fifth quintile	3.753	792	0.62 (0.57, 0.69)	0.88 (0.79, 0.99)
P-trend			<0.0001	0.0128
Nuts/seeds, oz				
First quintile	0.000	1019	1.00	1.00
Second quintile	0.066	958	0.95 (0.87, 1.04)	0.93 (0.85, 1.03)
Third quintile	0.154	840	0.82 (0.75, 0.90)	0.83 (0.75, 0.91)
Fourth quintile	0.285	907	0.90 (0.81, 0.98)	0.93 (0.85, 1.03)
Fifth quintile	0.987	919	0.90 (0.82, 0.99)	0.92 (0.83, 1.02)
P-trend			0.0097	0.1530
Legumes, cups				
First quintile	0.003	948	1.00	1.00
Second quintile	0.030	981	0.91 (0.83, 1.01)	1.03 (0.94, 1.13)
Third quintile	0.057	913	0.99 (0.89, 1.10)	0.97 (0.88, 1.07)
Fourth quintile	0.097	853	0.98 (0.88, 1.09)	0.91 (0.82, 1.01)
Fifth quintile	0.203	948	1.02 (0.91, 1.15)	0.99 (0.86, 1.09)
P-trend			0.1607	0.2004

[1]Model 1 was nutrient density adjusted; model 2 adjusted for variables in model 1 plus race-ethnicity, education, income, BMI, diabetes, hypertension, hormone replacement therapy, stroke, myocardial infarction, Alzheimer disease, cardiovascular disease, cancer, physical activity, stressful life events, social support, smoking, alcohol, and energy-adjusted intakes of SFAs, MUFAs, PUFAs, and *trans* fatty acids. One cup = 236.588 mL. oz, ounces (1 oz = 28.3495 g).

foods such as potatoes, bread, and rice can have enough protein to blunt or prevent increases in tryptophan concentrations.

Although the only previous longitudinal epidemiologic study to use global measures of carbohydrate consumption found no relation between dietary GI and depression, this was a study of intake during pregnancy and the prediction of postpartum depression 2–9 mo after giving birth (15). Our diverging results are likely attributable to differences in eating patterns (Japanese compared with Western), cohorts (pregnant compared with postmenopausal), and depressive subtype outcomes (postpartum compared with non–postpartum depression).

There are plausible mechanisms by which a high-GI diet could increase the risk of depression. The high consumption of refined starches and sugars is a risk factor for inflammation and cardiovascular disease (31), and these conditions have been implicated in the pathogenesis of depression (32). The consumption of high-GI diets could also lead to insulin resistance (33), which has been associated with a pattern of volumetric and neurocognitive deficits that are highly similar to those reported in individuals suffering from major depression (34). Another path by which high–glycemic load diets could contribute toward depression is through repeated acute spikes and troughs in blood glucose. The concepts of GI and glycemic load have been shown to provide physiologically valid estimates of postprandial glycemia and insulin demand in healthy individuals (35). Postprandial hyperglycemia and resultant compensatory hyperinsulinemia from high dietary glycemic load can lower plasma glucose to concentrations that compromise brain glucose, ∼70 mg/dL (3.8 mmol/L) (36), triggering the secretion of autonomic counterregulatory hormones such as adrenaline, cortisol, glucagon, and growth hormone (37). There is evidence to suggest that repeated hyperglycemia could induce a protective downregulation of blood-to-brain glucose transport, resulting in a lowered threshold for autonomic activation (38). Counterregulatory hormone responses can cause symptoms such as anxiety, irritability, and hunger, whereas manifestations of neuroglycopenia can include cognitive impairment, mood and behavioral changes, and fatigue (39). These symptoms have been found to be relatively common, with 37.9% of women from the UK general population reporting symptoms that they attributed to low blood sugar (40). These symptoms were also found to be relatively persistent. In an animal model of depression, insulin-induced hypoglycemia, lasting <2 h, was shown to result in depressive-like behaviors in mice, which persisted for 24–48 h (41).

Possible limitations of our study include the measurement of our dietary exposures and covariates from FFQs, instead of dietary biomarkers or food records, and the assessment of our outcome of depression from self-reported symptoms as opposed to psychiatric interviews. However, we would expect that any misclassification of exposure or outcome would have been random, resulting in nondifferential misclassification, which usually leads to bias toward the null hypothesis (42). The potential also exists for residual confounding from unmeasured confounders. The sample for this study was composed entirely of postmenopausal women, limiting the generalizability of our findings to other populations.

The results from this study suggest that high-GI diets could be a risk factor for depression in postmenopausal women. Randomized trials should be undertaken to examine the question of whether diets rich in low-GI foods, such as legumes, cereals high in viscous sticky fibers, and temperate-climate fruit, could serve as treatments and primary preventive measures for depression in postmenopausal women.

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