Low Carbohydrate–Diet Scores and Long-term Risk of Type 2 Diabetes Among Women With a History of Gestational Diabetes Mellitus: A Prospective Cohort Study

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OBJECTIVE

Low-carbohydrate diets (LCDs) may improve short-term glycemic control in patients with gestational diabetes mellitus (GDM), but the long-term effect on progression from GDM to type 2 diabetes mellitus (T2DM) is unknown. We aimed to examine the long-term risk of T2DM in association with a low-carbohydrate dietary pattern among women with a history of GDM.

RESEARCH DESIGN AND METHODS

Overall, 4,502 women with a history of GDM from the Nurses' Health Study II (NHSII) cohort, as part of the Diabetes & Women's Health (DWH) study, were followed up from 1991 to 2011. Overall, animal, or vegetable LCD scores, which represent adherence to different low-carbohydrate dietary patterns, were calculated using diet intake information assessed every 4 years since 1991 by validated food-frequency questionnaires. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs.

RESULTS

We documented 722 incident cases of T2DM during 68,897 person-years of observation. The multivariable-adjusted HRs (95% CIs) of T2DM, comparing the highest with lowest quintiles, were 1.36 (1.04–1.78) for overall LCD score (P = 0.003 for trend), 1.40 (1.06–1.84) for animal LCD score (P = 0.004 for trend), and 1.19 (0.91–1.55) for vegetable LCD score (P = 0.50 for trend).

CONCLUSIONS

Among women with a history of GDM, a low-carbohydrate dietary pattern, particularly with high protein and fat intake mainly from animal-source foods, is associated with higher T2DM risk, whereas a low-carbohydrate dietary pattern with high protein and fat intake from plant-source foods is not significantly associated with risk of T2DM.

Type 2 diabetes mellitus (T2DM) has become a worldwide epidemic, underscoring the importance of preventing T2DM as a public health priority (1). Women with a history of gestational diabetes mellitus (GDM), a common pregnancy complication, represent a group at high risk of T2DM (2). Specifically, women with GDM have sevenfold increased risk of developing T2DM compared with those with a

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normoglycemic pregnancy (3). Although GDM is detected during pregnancy, most women with GDM probably have reduced insulin secretion and/or chronic insulin resistance before pregnancy, and the glucose intolerance may deteriorate through their life span (2). The roles of dietary and lifestyle factors in modifying the natural course of the progression from GDM to overt T2DM remain to be elucidated in such a high-risk population. In previous studies, we found that higher diet quality and a physically active lifestyle are associated with lower risk of T2DM among women with prior GDM (4,5).

Low-carbohydrate diets (LCDs) are among the most popular diets that are claimed to promote weight loss (6). These diets are appealing because of not having to count calories or compromise the consumption of many palatable foods. However, LCDs are at risk for being nutritionally inadequate or imbalanced because they enforce restriction of food choices (7). These diets limit consumption of some healthful dietary components, such as whole grains, dietary fiber, fruit, and vegetables, and they can be high in animal fat and red meat, which have been associated with an increased risk of T2DM (8). Therefore, long-term adherence to LCDs, particularly those mainly based on animal-source foods, may have unfavorable effects on glucose homeostasis and increase the risk of T2DM. A previous study found a dietary pattern score representing moderately low carbohydrate, high animal protein, and high animal fat intakes was positively associated with T2DM risk (9).

Women with GDM are advised to limit carbohydrate intake during and after pregnancy as a key component of medical nutrition therapy. For instance, the Endocrine Society Clinical Practice Guideline suggests that women with GDM should limit carbohydrate intake to 35–45% of total calories (10). LCDs may improve short-term glycemic control in patients with GDM (11,12), but the long-term effect on the progression from GDM to T2DM is unknown. In this study, we examined the long-term risk of T2DM in association with three low-carbohydrate dietary patterns among women with a history of GDM, a population at high risk of T2DM.

RESEARCH DESIGN AND METHODS

Study Population

The study population is composed of women with a history of GDM in the Nurses' Health Study II (NHSII), as part of the ongoing Diabetes & Women's Health (DWH) study (13), which aims to identify determinants of the progression from GDM to T2DM. The NHSII, established in 1989, is an ongoing prospective cohort study of 116,430 female nurses aged 24–44 years at study initiation (14). The participants receive a biennial questionnaire to update information on health-related behaviors and disease outcomes. Follow-up for each questionnaire cycle is greater than 90%. This study was approved by the Partners Human Research Committee (Boston, MA), with participants' consent implied by the return of the questionnaires.

In this cohort, dietary information was collected first in 1991 and every 4 years thereafter using a semiquantitative food-frequency questionnaire (FFQ). Participants were eligible for inclusion in this analysis if they reported GDM before 1991 or incident GDM through the 2001 questionnaire. GDM was last captured on the 2001 questionnaire because most of the NHSII participants passed reproductive age. In a prior validation study among a subgroup of this cohort, 94% of GDM self-reports were confirmed by medical records (14). In a random sample of parous women without GDM, 83% reported a glucose screening test during pregnancy, and 100% reported frequent prenatal urine screenings, indicating a high level of GDM surveillance in this cohort (14). Participants were excluded from this analysis if they reported chronic disease (T2DM, cardiovascular disease, cancer) before their GDM pregnancy or before the return of their first post-GDM FFQ, had a multiple-birth pregnancy, or did not return any post-GDM FFQ.

Exposure Assessment

Every 4 years since 1991, the participants reported their usual intake (frequency ranging from never to >6 times/day) during the past year of a standard portion of each item in the FFQ. The reproducibility and validity of the FFQ has been extensively documented (15–17). We computed intakes of individual nutrients by multiplying the frequency of consumption of each food by the nutrient content of the specified portion based on food composition data from U.S. Department of Agriculture and data from manufacturers. Intakes of carbohydrate, fat, and protein were expressed as nutrient densities (i.e., percent of energy), and intakes of other nutrients were energy adjusted using the residual method (18). A previous validation study comparing energy-adjusted macronutrient intake assessed by the FFQ with four 1-week diet records found the Pearson correlation coefficients were 0.61 for total carbohydrates, 0.52 for total protein, and 0.54 for total fat (16).

To represent adherence to various low-carbohydrate dietary patterns, we calculated three LCD scores (i.e., overall LCD score, animal LCD score, and vegetable LCD score) for each participant, as previously described (19,20). Briefly, we divided study participants into 11 strata according to each of fat, protein, and carbohydrate intake, expressed as percentages of energy. We assigned them 0–10 points for increasing intake of total fat, 0–10 points for increasing intake of total protein, and inversely, 10–0 points for increasing intake of carbohydrates. Then we summed points for the three macronutrients to create an overall LCD score, which ranged from 0 to 30. Similarly, we also created an animal LCD score to represent preferential substitution of carbohydrates with fat and protein from animal sources and a vegetable LCD score to represent preferential substitution of carbohydrates with fat and protein from vegetable sources. The animal LCD score was based on intakes of carbohydrate, animal protein, and animal fat, and the vegetable LCD score was based on intakes of carbohydrate, vegetable protein, and vegetable fat. A higher score reflects a higher intake of fat and protein and a lower intake of carbohydrate, indicating closer adherence to a low-carbohydrate dietary pattern.

Covariate Assessment

Information on age, weight, race/ethnicity, family history of diabetes, smoking status, age at first birth, use of oral contraceptives, and menopausal status has been collected on biennial questionnaires. Parity was defined as the number of pregnancies lasting greater than 6 months. Self-reported weight was highly

correlated with a measured weight (r = 0.97) in a previous validation study (21). BMI was computed as weight in kilograms divided by height in meters squared. Total physical activity was ascertained by frequency of engaging in common recreational activities, from which MET h/week were derived. In a previous validation study in this cohort, the correlation coefficients of physical activity as reported in 1-week recalls and diaries with that reported on the questionnaires were 0.79 and 0.62, respectively (22).

Ascertainment of Outcome

Participants reporting physician-diagnosed T2DM on each biennial questionnaire were mailed a supplemental questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy to confirm self-reported diagnoses. Confirmed T2DM was defined according to the American Diabetes Association criteria (23): *1*) one or more classic symptoms (excessive thirst, polyuria, unintentional weight loss, hunger) plus elevated glucose levels (fasting plasma glucose concentration ≥7.0 mmol/L or random plasma glucose ≥11.1 mmol/L), *2*) no symptoms reported but two or more elevated plasma glucose concentrations on more than one occasion (fasting ≥7.0 mmol/L, random ≥11.1 mmol/L, 2-h oral glucose tolerance test ≥11.1 mmol/L), or *3*) treatment with insulin or oral hypoglycemic agent. Before 1998, fasting plasma glucose ≥7.8 mmol/L was used instead of ≥7.0 mmol/L for the diagnosis of diabetes according to the criteria of National Diabetes Data Group (24). A subgroup validation study conducted in a similar cohort of U.S. female nurses reported a high accuracy rate of 98% by comparing our classification against medical records (25).

Statistical Analysis

In this analysis, we defined baseline as the questionnaire period in which participants first reported a GDM pregnancy. The baseline characteristics of the cohort were age adjusted according to 5-year age-groups by direct standardization to the entire cohort. Comparisons among quintiles of LCD scores were performed using ANOVA for continuous variables and the χ^2 test for categorical variables.

We computed follow-up time from the date of GDM diagnosis to the date of T2DM diagnosis, death, or the return of the 2011 questionnaire, whichever came first. Updating of exposure status ceased if a participant reported incident chronic diseases (cardiovascular disease, cancer). We carried forward missing exposure data from the most recent questionnaire for which data were captured. Exposure data were missing for less than 7% of the participants. To represent long-term habitual diet after GDM and reduce measurement error (26), we calculated a cumulative average LCD score based on the information from each post-GDM FFQ during the study period.

We used Cox proportional hazards models to estimate the hazard ratios (HRs) and 95% CIs of T2DM risk in relation to quintiles of LCD scores. The covariates adjusted in the models included age (months), parity (1, 2, 3, ≥4), age at first birth (12–24, 25–29, ≥30 years), race/ethnicity (Caucasian, African American, Hispanic, Asian, other), family history of diabetes (yes or no), oral contraceptive use (current, former, never), menopausal status (premenopausal or postmenopausal), cigarette smoking (current, former, never), alcohol intake (0, 0.1–4.9, 5.0–14.9, ≥15.0 g/day), total energy intake (quintiles), and glycemic index (quintiles). All of the time-varying covariates were updated during the follow-up and were modeled as time-varying variables in the models. We included BMI (<23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0 kg/m^2) in the model separately because BMI may be an intermediate variable between the LCD scores and incident T2DM. We also performed mediation analyses to estimate the proportion of the association between the LCD scores and incident T2DM that is explained by BMI (modeled continuously) (27), using a publicly available SAS macro (28).

To evaluate potential effect modification, we performed stratified analyses according to age (<40 or ≥40 years), family history of diabetes (yes or no), obesity (BMI <30 or ≥30 kg/m^2), and time since the first GDM pregnancy (>10 or ≤10 years). We conducted interaction tests via multiplicative interaction terms in the multivariable models. All statistical analyses were performed with SAS 9.3 software (SAS Institute Inc., Cary, NC). $P < 0.05$ was considered statistically significant.

RESULTS

We documented 722 incident T2DM cases from 4,502 participants with a history of GDM (3,243 prevalent cases of GDM in 1991 and 1,259 incident GDM cases developed between 1991 and 2001), contributing 68,897 person-years of observation. The average number of pregnancies with GDM was 2.5 among women who had a diagnosis of T2DM and 2.0 among women who did not have a diagnosis of T2DM. At baseline, women with a higher overall LCD score were more likely to be white, currently smoking, and less physically active; to have a higher BMI and family history of diabetes; and to consume more cholesterol and heme iron but less total calories and dietary fiber (Table 1). By food group categories, they consumed more red meat and less fruits, vegetables, and whole grains. We observed similar results for the animal LCD score (Supplementary Table 1). In contrast, participants with a higher vegetable LCD score consumed more nuts, vegetables, and whole grains but less calcium than those with a lower score (Supplementary Table 2). Each of these three LCD scores was inversely associated with dietary glycemic index and glycemic load. There was a very high correlation between the overall LCD score and the animal LCD score (r = 0.93, $P < 0.001$), and their correlations with vegetable LCD score were also significant (r = 0.49 for correlation between overall and vegetable LCD scores, $P < 0.001$; r = 0.20 for correlation between animal and vegetable LCD scores, $P < 0.001$). The animal LCD score had the most statistical variation (standard deviation [SD] 8.1), followed by overall LCD score (SD 7.5) and vegetable LCD score (SD 5.6), although they all had a mean score of 15 in this study population.

Overall and animal LCD scores were positively and significantly associated with risk of T2DM among women with a history of GDM, whereas the vegetable LCD score was not significantly associated with the risk (Table 2). The multivariable-adjusted HRs (95% CIs) of T2DM comparing the highest with lowest quintiles were 2.13 (1.65–2.76) for

Table 1—Age-standardized baseline characteristics according to quintiles of LCD scores among women with a history of GDM[a,b]

	Quintiles of overall LCD score				
Characteristic	Quintile 1 (*n* = 976)	Quintile 2 (*n* = 734)	Quintile 3 (*n* = 988)	Quintile 4 (*n* = 955)	Quintile 5 (*n* = 849)
Low carbohydrate intake (%)[c]	0.3	1.7	2.4	9.7	33.7
Age (years)	38.3 (4.7)	37.8 (4.6)	37.8 (4.7)	37.8 (4.8)	38.1 (4.9)
Age at first birth (years)	27.8 (4.9)	27.6 (4.7)	27.4 (4.8)	27.4 (4.8)	27.3 (5.0)
Parity >1 (%)	79.6	79.5	83.6	81.5	80.8
White race (%)	89.3	92.1	93.4	94.5	93.3
Family history of diabetes (%)	24.5	26.5	25.8	25.1	33.4
Current oral contraceptive use (%)	8.3	8.5	9.0	7.8	8.9
Current smoking (%)	11.4	7.5	9.5	11.7	15.3
Alcohol (g/day)	1.9 (3.7)	2.2 (4.2)	2.7 (5.7)	2.8 (5.4)	2.0 (4.3)
BMI (kg/m^2)	25.4 (5.5)	26.2 (5.8)	26.6 (6.0)	27.4 (6.2)	29.1 (6.9)
Physical activity (MET h/week)	19.2 (23.1)	16.4 (20.4)	16.6 (19.4)	16.5 (22.0)	15.4 (19.1)
Total calories (kcal/day)	1,997.1 (581.4)	1,942.5 (546.9)	1,927.5 (564.6)	1,865.9 (547.3)	1,816.1 (571.1)
Carbohydrates (% energy)	57.3 (5.9)	52.3 (4.9)	49.6 (4.6)	46.0 (5.0)	42.0 (6.4)
Total protein (% energy)	17.0 (2.9)	19.0 (3.0)	19.3 (3.1)	20.2 (3.2)	21.6 (2.9)
Animal protein (% energy)	11.6 (3.0)	13.7 (3.1)	14.2 (3.2)	15.2 (3.4)	16.9 (3.3)
Vegetable protein (% energy)	5.4 (1.4)	5.3 (1.0)	5.1 (1.0)	5.0 (1.0)	4.7 (1.0)
Total fat (% energy)	27.3 (4.7)	29.8 (4.7)	31.9 (4.4)	34.4 (4.9)	36.9 (5.3)
Animal fat (% energy)	14.3 (4.0)	16.4 (3.6)	17.8 (3.5)	19.5 (4.0)	22.1 (4.9)
Vegetable fat (% energy)	13.0 (3.7)	13.5 (3.9)	14.1 (4.0)	14.8 (4.6)	14.8 (4.2)
SFA (% energy)	9.5 (2.1)	10.4 (2.1)	11.2 (2.0)	12.1 (2.2)	13.0 (2.4)
MUFA (% energy)	10.4 (2.0)	11.4 (2.1)	12.2 (2.0)	13.2 (2.3)	14.3 (2.4)
PUFA (% energy)	4.9 (1.2)	5.3 (1.3)	5.6 (1.3)	6.0 (1.5)	6.3 (1.5)
Trans fat (% energy)	1.4 (0.5)	1.5 (0.5)	1.7 (0.6)	1.8 (0.6)	1.9 (0.6)
Cholesterol (mg/day)[d]	198.0 (58.2)	229.8 (56.0)	245.2 (54.4)	268.3 (66.6)	299.6 (84.0)
Total fiber (g/day)[d]	19.7 (6.5)	19.1 (4.8)	18.5 (4.8)	17.7 (4.5)	16.7 (4.2)
Glycemic index[d]	55.0 (3.1)	54.1 (3.1)	53.7 (3.0)	53.2 (3.4)	52.8 (4.1)
Glycemic load[d]	141.5 (18.1)	127.3 (15.4)	119.8 (13.9)	110.3 (14.9)	100.5 (18.6)
Heme iron (mg/day)[d]	0.9 (0.3)	1.1 (0.3)	1.1 (0.3)	1.3 (0.4)	1.5 (0.4)
Red meat (servings/day)	0.8 (0.6)	0.9 (0.6)	1.0 (0.6)	1.1 (0.6)	1.3 (0.7)
Poultry (servings/day)	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.4)
Fish (servings/day)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.3 (0.2)
Eggs (servings/day)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)
Dairy (servings/day)	2.8 (2.3)	3.0 (2.3)	2.8 (2.0)	2.7 (1.9)	2.7 (2.1)
Fruits (servings/day)	1.5 (1.2)	1.4 (0.9)	1.3 (0.9)	1.1 (0.8)	0.9 (0.7)
Vegetables (servings/day)	3.7 (2.4)	3.6 (2.0)	3.5 (2.1)	3.5 (2.0)	3.4 (2.0)
Nuts (servings/day)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.5)	0.3 (0.4)
Legumes (servings/day)	0.5 (0.4)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)
Whole grains (servings/day)	1.2 (1.1)	1.2 (1.0)	1.1 (1.1)	0.9 (0.9)	0.9 (0.8)
SSBs (servings/day)	1.0 (1.4)	0.5 (0.9)	0.4 (0.6)	0.2 (0.5)	0.2 (0.4)

Data are mean (SD) unless otherwise specified. All comparisons across quintiles are significant except age at first birth, multiparity (parity >1), current oral contraceptive use, and nut consumption. MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; SSBs, sugar-sweetened beverages. [a]Baseline was defined as 1991 for prevalent GDM and the year of the index pregnancy for incident GDM. [b]The baseline characteristics of the cohort were age adjusted according to 5-year age-groups by direct standardization to the entire cohort. [c]Defined as carbohydrate intake <40% of energy. [d]Value is energy adjusted using the residual method (18).

overall LCD score ($P < 0.001$ for trend), 2.18 (1.68–2.83) for animal LCD score ($P < 0.001$ for trend), and 1.29 (1.00–1.67) for the vegetable LCD score ($P = 0.14$ for trend). The significant associations of overall and animal LCD scores with T2DM risk were attenuated but remained significant after additional adjustment for updated BMI, with the HRs (95% CIs) comparing the highest versus the lowest quintiles of 1.36 (1.04–1.78; $P = 0.003$ for trend) for overall LCD score and 1.40 (1.06–1.84; $P = 0.004$ for trend) for the animal LCD score. Mediation analyses estimated that updated BMI explained 66% (95% CI 42–89; $P < 0.001$) and 64% (95% CI 42–86; $P < 0.001$) of the total effects of the overall LCD score and the animal LCD score on T2DM risk, respectively. In addition, the associations of the overall LCD score and

Table 2—Association between LCD scores and risk of T2DM among women with a history of GDM

	Quintiles of LCD scores					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
Overall LCD score						
Median score	5	10	15	19	25	–
Cases of T2DM (*n*)	124	99	144	141	214	–
Person-years	14,821	11,697	15,563	11,973	14,843	–
Age-adjusted model	1.00 (reference)	1.01 (0.76–1.35)	1.11 (0.85–1.44)	1.44 (1.10–1.87)	1.89 (1.48–2.42)	<0.001
Multivariable model[a]	1.00 (reference)	1.07 (0.80–1.44)	1.24 (0.95–1.63)	1.66 (1.26–2.19)	2.13 (1.65–2.76)	<0.001
Multivariable model + BMI[b]	1.00 (reference)	0.95 (0.70–1.30)	1.02 (0.77–1.36)	1.28 (0.96–1.71)	1.36 (1.04–1.78)	0.003
Animal LCD score						
Median score	4	10	15	20	26	–
Cases of T2DM (*n*)	114	107	146	142	213	–
Person-years	14,426	13,022	14,357	12,727	14,367	–
Age-adjusted model	1.00 (reference)	0.97 (0.73–1.29)	1.30 (1.00–1.70)	1.44 (1.10–1.89)	1.95 (1.52–2.50)	<0.001
Multivariable model[a]	1.00 (reference)	1.04 (0.77–1.39)	1.40 (1.07–1.84)	1.63 (1.23–2.15)	2.18 (1.68–2.83)	<0.001
Multivariable model + BMI[b]	1.00 (reference)	0.97 (0.71–1.32)	1.12 (0.84–1.50)	1.18 (0.88–1.58)	1.40 (1.06–1.84)	0.004
Vegetable LCD score						
Median score	8	12	15	18	22	–
Cases of T2DM (*n*)	143	147	144	128	160	–
Person-years	15,212	12,306	13,185	12,800	15,394	–
Age-adjusted model	1.00 (reference)	1.32 (1.03–1.70)	1.18 (0.92–1.53)	1.20 (0.92–1.56)	1.13 (0.88–1.45)	0.58
Multivariable model[a]	1.00 (reference)	1.45 (1.12–1.88)	1.33 (1.02–1.72)	1.29 (0.99–1.69)	1.29 (1.00–1.67)	0.14
Multivariable model + BMI[b]	1.00 (reference)	1.38 (1.05–1.81)	1.24 (0.94–1.63)	1.14 (0.86–1.51)	1.19 (0.91–1.55)	0.50

Data are HR (95% CI) unless noted otherwise. [a]Covariates in the multivariable model included age (months), parity (1, 2, 3, ≥4), age at first birth (12–24, 25–29, ≥30 years), race/ethnicity (Caucasian, African American, Hispanic, Asian, other), family history of diabetes (yes or no), oral contraceptive use (current, former, never), menopausal status (premenopausal or postmenopausal), cigarette smoking (never, former, current), alcohol intake (0, 0.1–4.9, 5.0–14.9, ≥15.0 g/day), physical activity (quintiles), total energy intake (quintiles), and glycemic index. All the time-varying covariates were updated during the follow-up and were modeled as time-varying variables in the models. [b]BMI, as a time-varying variable, was modeled as <23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, 35.0–39.9, or ≥40.0 kg/m^2.

the animal LCD score with T2DM risk were not significantly altered by age, family history of diabetes, obesity status, and time since GDM pregnancy (all $P >$ 0.10 for interaction). Similar results were observed in sensitivity analyses by skipping questionnaire cycles in which FFQs were not returned or carrying forward missing exposure data from the participant's cumulative average intake of all past post-GDM FFQs instead of carrying forward missing exposure data from the most recent post-GDM FFQ available as in the current analysis.

CONCLUSIONS

In this prospective cohort study with up to 20 years of follow-up, we observed that a dietary score representing a low-carbohydrate, high–animal protein, and high–animal fat dietary pattern was significantly and positively associated with T2DM risk among women with a history of GDM. These associations were partly explained by BMI. By contrast, a dietary score representing a low-carbohydrate, high–vegetable protein, and high–vegetable fat dietary pattern was not associated with the risk of developing T2DM. The observed associations were not significantly modified by age, family history of diabetes, smoking, obesity status, or time since the first GDM pregnancy.

Previous studies examining the effects of carbohydrate restriction on glucose metabolism have yielded conflicting results. A nonrandomized study reported that carbohydrate restriction in patients with diet-controlled GDM resulted in improved glycemic control and less need for insulin therapy after 6 weeks of diet therapy (11). However, LCD treatment did not significantly reduce the need for insulin therapy among women with GDM in a recent randomized controlled trial with 4 months of follow-up (12). In addition, several randomized controlled trials have shown that LCDs seem to yield a significant reduction in blood glucose concentrations at 6 months after the intervention but that the reduction becomes nonsignificant at 12 months (29–33).

Women who follow low-carbohydrate dietary patterns consume less carbohydrate and more fat and protein that are naturally needed to compensate energy requirements. A previous study (34) showed a null association of quantity of carbohydrate intake with T2DM risk. The observed positive associations of overall and animal LCD scores with risk of T2DM in this study may be at least partly owing to some detrimental

effects of a high content of animal fat and/or animal protein. Previous studies in animal models and in humans show that higher intake of dietary animal fat can result in impaired glucose tolerance and T2DM (35,36). Higher intake of animal protein was associated with an increased risk of T2DM (37–39). Moreover, a meal rich in animal protein, compared with a meal rich in vegetable protein, results in higher plasma concentrations of branched-chain amino acids (40), which have been recently associated with insulin resistance and the development of T2DM in several metabolomics studies (41,42).

Several food groups, including red meat, vegetables, fruits, and whole grains, may contribute to the variability of the LCD scores and account for the observed associations. Red meat is a major dietary source of animal protein and animal fat in the Western diet. In this study, women with a higher overall or animal LCD score had a greater consumption of red meat than those with a lower score. Higher consumption of red meat has been previously associated with an increased risk of T2DM (43). On the other hand, women with a higher overall or animal LCD score, compared with those with a lower score, had a lower consumption of fruits, vegetables, and whole grains, which have been inversely associated with the risk of T2DM in previous studies (44,45).

Our study has several strengths, including the prospective cohort design that establishes the temporal direction of the associations, the large sample size, the long-term follow-up, the high response rates ($>$ 90%) of each questionnaire cycle in both the entire cohort and the subcohort members included in this study, and the detailed prospective dietary assessments with the extensively validated FFQs (15–17). All the study participants were registered nurses, reducing the potential confounding by educational attainment or differential access to health care.

We acknowledge that there are several limitations. First, misclassification of dietary intakes of carbohydrate, fat, and protein is possible. However, the misclassification would be nondifferential due to the prospective nature of the dietary assessment with regard to incident T2DM; therefore, our findings may underestimate the true associations. Furthermore, the use of cumulative averages of dietary intakes for participants with longitudinal FFQs reduces random error.

Second, screening bias may exist if more health-conscious women regularly visit a physician, thus increasing their chance of receiving a medical diagnosis. However, in our sensitivity analyses, similar results were seen when we restricted cases to symptomatic T2DM, minimizing concerns for this bias.

Third, our study population consisted mostly of Caucasian American women. Thus, the direct generalization of our findings to other populations whose major food sources of macronutrients are different may be limited. Among our participants, Asian women had lower LCD scores (i.e., higher carbohydrate intake) compared with Caucasian, African American, and Hispanic women. In contrast to findings among U.S. men (9) and women (46), a recent study among the Japanese population, in which white rice consumption is high, found a LCD score was associated with lower risk of T2DM (47). The association between LCD scores and risk of T2DM across different race/ethnic groups warrants further evaluation.

In conclusion, among women with a history of GDM, a low-carbohydrate dietary pattern, particularly with high protein and fat intake mainly from animal-source foods, is associated with higher T2DM risk, whereas a low-carbohydrate dietary pattern with high protein and fat from plant-source foods is not associated with risk of T2DM. Women with a history of GDM who follow a low-carbohydrate dietary pattern may consider consuming plant sources rather than animal sources of protein and fat to minimize their future risk of T2DM.

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References

1. Herman WH, Zimmet P. Type 2 diabetes: an epidemic requiring global attention and urgent action. Diabetes Care 2012;35:943–944
2. Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: risks and management during and after pregnancy. Nat Rev Endocrinol 2012; 8:639–649
3. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009;373:1773–1779
4. Bao W, Tobias DK, Bowers K, et al. Physical activity and sedentary behaviors associated with risk of progression from gestational diabetes mellitus to type 2 diabetes mellitus: a prospective cohort study. JAMA Intern Med 2014; 174:1047–1055
5. Tobias DK, Hu FB, Chavarro J, Rosner B, Mozaffarian D, Zhang C. Healthful dietary patterns and type 2 diabetes mellitus risk among women with a history of gestational diabetes mellitus. Arch Intern Med 2012;172:1566–1572
6. Malik VS, Hu FB. Popular weight-loss diets: from evidence to practice. Nat Clin Pract Cardiovasc Med 2007;4:34–41
7. Adam-Perrot A, Clifton P, Brouns F. Low-carbohydrate diets: nutritional and physiological aspects. Obes Rev 2006;7:49–58
8. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet 2014;383:1999–2007
9. de Koning L, Fung TT, Liao X, et al. Low-carbohydrate diet scores and risk of type 2 diabetes in men. Am J Clin Nutr 2011;93:844–850
10. Blumer I, Hadar E, Hadden DR, et al. Diabetes and pregnancy: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2013;98:4227–4249
11. Major CA, Henry MJ, De Veciana M, Morgan MA. The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. Obstet Gynecol 1998;91:600–604
12. Moreno-Castilla C, Hernandez M, Bergua M, et al. Low-carbohydrate diet for the treatment of gestational diabetes mellitus: a randomized controlled trial. Diabetes Care 2013; 36:2233–2238
13. Zhang C, Hu FB, Olsen SF, et al.; DWH study team. Rationale, design, and method of the Diabetes & Women's Health study–a study of

long-term health implications of glucose intolerance in pregnancy and their determinants. Acta Obstet Gynecol Scand 2014;93:1123–1130
14. Solomon CG, Willett WC, Carey VJ, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA 1997;278: 1078–1083
15. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65
16. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–199
17. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–867
18. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27
19. Halton TL, Willett WC, Liu S, et al. Low-carbohydrate-diet score and the risk of coronary heart disease in women. N Engl J Med 2006;355:1991–2002
20. Bao W, Bowers K, Tobias DK, et al. Prepregnancy low-carbohydrate dietary pattern and risk of gestational diabetes mellitus: a prospective cohort study. Am J Clin Nutr 2014;99:1378–1384
21. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–473
22. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23:991–999
23. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–1197
24. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–1057
25. Manson JE, Rimm EB, Stampfer MJ, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 1991;338:774–778
26. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–540
27. Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Stat Med 1997;16:1515–1527
28. Hertzmark E, Pazaris M, Spiegelman D. The SAS MEDIATE Macro [article online], 2012. Available from http://www.hsph.harvard.edu/faculty/donna-spiegelman/software/mediate. Accessed 23 December 2014
29. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:285–293
30. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082–2090
31. Davis NJ, Tomuta N, Schechter C, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. Diabetes Care 2009;32:1147–1152
32. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA 2005;293:43–53
33. Bazzano LA, Hu T, Reynolds K, et al. Effects of low-carbohydrate and low-fat diets: a randomized trial. Ann Intern Med 2014;161:309–318
34. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr 2004;80:348–356
35. Lichtenstein AH, Schwab US. Relationship of dietary fat to glucose metabolism. Atherosclerosis 2000;150:227–243
36. Thanopoulou AC, Karamanos BG, Angelico FV, et al. Dietary fat intake as risk factor for the development of diabetes: multinational, multicenter study of the Mediterranean Group for the Study of Diabetes (MGSD). Diabetes Care 2003;26:302–307
37. Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. Diabetes Care 2010;33:43–48
38. van Nielen M, Feskens EJ, Mensink M, et al.; InterAct Consortium. Dietary protein intake and incidence of type 2 diabetes in Europe: the EPIC-InterAct Case-Cohort Study. Diabetes Care 2014;37:1854–1862
39. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the Women's Health Study. Diabetes Care 2004;27:2108–2115
40. Brandsch C, Shukla A, Hirche F, Stangl GI, Eder K. Effect of proteins from beef, pork, and turkey meat on plasma and liver lipids of rats compared with casein and soy protein. Nutrition 2006;22:1162–1170
41. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab 2009;9:311–326
42. Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. Nat Med 2011;17:448–453
43. Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. Am J Clin Nutr 2011;94:1088–1096
44. Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. BMJ 2010;341: c4229
45. de Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. PLoS Med 2007;4:e261
46. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. Am J Clin Nutr 2008;87:339–346
47. Nanri A, Mizoue T, Kurotani K, et al.; Japan Public Health Center-Based Prospective Study Group. Low-carbohydrate diet and type 2 diabetes risk in Japanese men and women: the Japan Public Health Center-Based Prospective Study. PLoS One 2015;10:e0118377