A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes[1–3]

Katherine Bowers, Deirdre K Tobias, Edwina Yeung, Frank B Hu, and Cuilin Zhang

ABSTRACT

Background: Fatty acids play a vital role in glucose homeostasis; however, studies on habitual dietary fat intakes and gestational diabetes mellitus (GDM) risk are limited and provide conflicting findings.

Objective: We determined whether the total amount and the type and source of prepregnancy dietary fats are related to risk of GDM.

Design: A prospective study was conducted in 13,475 women who reported a singleton pregnancy between 1991 and 2001 in the Nurses' Health Study II. In these women, 860 incident GDM cases were reported. The adjusted RR of GDM was estimated for quintiles of total fat, specific fat, and the source of fat intakes by pooled logistic regression.

Results: Higher animal fat and cholesterol intakes were significantly associated with increased GDM risk. Across increasing quintiles of animal fat, RRs (95% CIs) for GDM were 1.00 (reference), 1.55 (1.20, 1.98), 1.43 (1.09, 1.88), 1.40 (1.04, 1.89), and 1.88 (1.36, 2.60) (P-trend = 0.05). Corresponding RRs (95% CIs) for dietary cholesterol were 1.00 (reference), 1.08 (0.84, 1.32), 1.02 (0.78, 1.29), 1.20 (0.93, 1.55), and 1.45 (1.11, 1.89) (P-trend = 0.04). The substitution of 5% of energy from animal fat for an equal percentage of energy from carbohydrates was associated with significantly increased risk of GDM [RR (95% CI): 1.13 (1.08, 1.18); $P < 0.0001$]. No significant associations were observed between dietary polyunsaturated fat, monounsaturated fat, or *trans* fat intakes and GDM risk.

Conclusion: Higher prepregnancy intakes of animal fat and cholesterol were associated with elevated GDM risk. *Am J Clin Nutr* 2012;95:446–53.

INTRODUCTION

GDM[4] is one of the most common pregnancy complications that affects ≤14% of pregnancies in high-risk populations (1). Although details of the underlying mechanism remain unclear, existing data suggest that the main defect of GDM is relatively diminished insulin secretion coupled with pregnancy-induced insulin resistance (2). Therefore, factors that contribute to insulin resistance or impaired insulin secretion before pregnancy could increase risk of GDM. A number of prepregnancy dietary and lifestyle factors have been recently related to GDM risk (3–7).

Fatty acids play a vital role in glucose homeostasis. Increased plasma free fatty acids may cause a dose-dependent inhibition of insulin-stimulated glucose uptake and, therefore, contribute to insulin resistance (8). Fatty acids also play a role in the alteration of cell membrane function (9), enzyme activity (10), and gene expression (11). Studies on dietary fatty acids and GDM risk are limited; the majority of studies have focused on fat intake during pregnancy, and the findings have been inconsistent (12–17). For instance, the substitution of total fat for carbohydrates during early pregnancy was associated with increased risk of GDM and impaired glucose tolerance in a prospective cohort of US women (15), whereas a lower total fat intake in pregnancy was related to higher GDM and impaired glucose tolerance risk in Chinese women (12). Other studies identified no association between total fat intake and GDM risk (13, 16). Also, the majority of available studies were small, retrospective, or provided insufficient control for dietary and nondietary potential confounding variables. In the current study, we systematically investigated the association of prepregnancy dietary fat intake, including specific fats as well as the source of fats (animal compared with vegetable fat), with risk of GDM in women in a large prospective cohort. We also considered the potential impact of other dietary and nondietary risk factors for GDM.

SUBJECTS AND METHODS

Study population

The Nurses' Health Study II is a prospective cohort study of 116, 671 female US nurses who were recruited between 22 and 44 y of age beginning in 1989. The cohort was and continues to be

[1] From the Epidemiology Branch, Division of Epidemiology, Statistics and Prevention Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD (KB, EY, and CZ); the Departments of Epidemiology and Nutrition, Harvard School of Public Health, Boston, MA (DKT and FBH); and the Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (FBH).

[2] Supported by research grants CA50385 and DK58845 from the NIH and the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH (KB, CZ, and EY).

[3] Address correspondence to C Zhang (e-mail: zhangcu@mail.nih.gov) or K Bowers (e-mail: bowerska2@mail.nih.gov) at Epidemiology Branch, Division of Epidemiology, Statistics, and Preventive Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, 6100 Executive Boulevard, Room 7B03, Rockville, MD 20852.

[4] Abbreviations: ABCA1, ATP-binding cassette transporter, subfamily A member 1; FFQ, food-frequency questionnaire; GDM, gestational diabetes mellitus.

Received September 6, 2011. Accepted for publication November 4, 2011.
First published online January 4, 2012; doi: 10.3945/ajcn.111.026294.

followed by biennial mailed questionnaires to update data on health-related behaviors and to identify incident disease. FFQs are mailed to participants every 4 y. The follow-up rate has been ~90% for every 2-y period (18). Women who reported a pregnancy that lasted ≥6 mo between 1991 and 2001 were included in the study. Women were excluded from the current analyses if they reported a multiple gestation, an implausible total energy intake (<500 or >3500 kcal/d), a diagnosis of diabetes, GDM, cancer, or cardiovascular disease, being in menopause at baseline, or missing information on age or vital status. The final analytic population included 13,475 women.

Ascertainment of GDM

GDM cases were identified on the basis of self-reported information on the biennial questionnaires through 2001. The validity of a self-reported diagnosis of GDM has been shown against medical record reviews (18). Briefly, of 114 women who corroborated their first diagnosis of GDM in a singleton pregnancy between 1989 and 1991 on a supplemental questionnaire, 94% of women were confirmed to have a physician diagnosis. Supplementary questionnaires were also sent to 100 women who reported a pregnancy uncomplicated by GDM during the same interval. Of 93 responders who confirmed a singleton pregnancy during this period, 83% of women reported a glucose loading test, and all women (100%) reported frequent urine screenings in pregnancy, which was consistent with a high degree of surveillance in this cohort (18).

Dietary assessment

Dietary intake is collected by a 133-item semiquantitative FFQ every 4 y. Information on the average frequency of consumption of selected foods and beverages during the previous year is reported. Intakes of total and specific fats as well as the source of fats are calculated as the sum of the contributions from all foods. The food-composition database used to calculate the nutrient values is based primarily on USDA data (19) and supplemented with data from manufacturers. Participants reported the use and dose of multivitamin supplements. To calculate the percentage of energy contributed by each type of fat, we divided the energy intake for each fat by the total caloric intake. The validity and reliability of the FFQ to assess nutrient intakes were measured in a similar cohort (Nurses' Health Study I) (20). For example, comparisons of the questionnaire to a series of four 1-wk dietary records identified correlation coefficients of ~0.5 for various types of fats and total fat intakes (20).

Measurement of nondietary factors

Information on sociodemographic, clinical, and lifestyle information was collected at baseline and updated every 2 y. BMI (in kg/m^2) was calculated by self-reported weight and height (weight divided by the square of height). In a similar cohort, self-reported body weight was highly correlated ($r = 0.96$) with technician-measured weight (18, 21). Physical activity was assessed in 1989, 1991, and 1997. Participants were asked to report weekly activities for each of the following categories: walking or hiking outdoors, jogging, running, bicycling, lap swimming, tennis, squash, or racquetball playing, calisthenics, and other forms of recreation. From this information, the weekly energy expenditure in metabolic equivalent task hours was calculated and used to calculate the cumulative average of total recreational physical activity in the analyses. A family history of diabetes and other diseases was reported at baseline (1989).

Statistical analyses

All statistical analyses were performed with SAS software (version 9.1; SAS Institute). Means with SDs for continuous baseline characteristics and proportions for categorical characteristics were calculated by quintiles of total fat, dietary cholesterol, animal fat, and vegetable fat and characterized by their nutrient density or percentage energy from total calories (except cholesterol, which was in mg). Total, saturated, monounsaturated, polyunsaturated, and *trans* unsaturated fat, the ratio of polyunsaturated to saturated fat, total omega-3 and omega-6 fatty acids, and animal, vegetable, and dairy fat were characterized as the nutrient density (except cholesterol) and analyzed by using a cumulative average measurement of fat intake before GDM diagnosis. For example, the 1991 intake was used for the follow-up between 1991 and 1995, and the average of the 1991 and 1995 intakes was used for the follow-up between 1995 and 1999, to reduce the within-person variation as well as to represent the habitual intake of dietary factors (22).

In multivariate models, total fat, fat subtypes, and the source of fats (animal compared with vegetable fat) were expressed as the nutrient density (percentage of calories from fat) and modeled as quintiles of intake. Quintiles were defined by the distribution of each nutrient at baseline. The significance of linear trends across categories of dietary intake was evaluated by using the median value for each category of dietary intake and analyzed as a continuous variable in multivariate models. Pooled logistic regression was used to estimate the RR of incident GDM for a given dietary fat exposure. Multivariate models were adjusted for age, parity, current smoking, BMI, physical activity, family history of diabetes, alcohol, race, and total calories. Additional dietary adjustments included cereal fiber and mutual adjustment for the specific fatty acids or source of fats.

To evaluate the effects of the substitution of specific types of fatty acids for carbohydrates, continuous nutrient densities were simultaneously included in multivariate models. By including all types of fatty acids in addition to protein, alcohol, and total calories concurrently, the coefficients could be interpreted as the effect of exchanging energy from a specific fat for the same amount of energy from carbohydrates. Additional models to evaluate the substitution of one type of fat for another also included carbohydrates while excluding the variable for a specific or source of fat. For instance, in one model we included energy from carbohydrates, protein, alcohol, and vegetable fat to estimate the effect of vegetable fat in exchange for the energy from animal fat. To evaluate the effect modification by some major risk factors of GDM, including BMI (<25 compared with ≥25), parity (parous compared with nulliparous), physical activity (highest 2 quintiles compared with lowest 3 quintiles), family history of diabetes (yes compared with no), and current cigarette-smoking status (yes compared with no), we conducted stratified analyses by these factors and estimated *P* values for interaction via multiplicative interaction terms in the multivariate models.

TABLE 1
Intercorrelations in energy-adjusted baseline intakes of fatty acid residuals, cholesterol, and animal fat[1]

	Total	SFA	MUFA	PUFA	EPA	DHA	Linoleic	α-Linolenic	*trans*	Cholesterol	Animal
Total	1	0.87	0.96	0.58	−0.13	−0.16	0.58	0.49	0.64	0.41	0.72
SFA		1	0.76	0.19	−0.19	−0.23	0.19	0.28	0.49	0.40	0.85
MUFA			1	0.52	−0.13	−0.17	0.54	0.38	0.71	0.35	0.64
PUFA				1	0.04	0.06	0.99	0.75	0.32	0.12	0.02
EPA					1	0.92	−0.05	0.04	−0.20	0.18	−0.07
DHA						1	−0.04	0.04	−0.23	0.26	−0.08
Linoleic							1	0.71	0.35	0.07	0.0004
α-Linolenic								1	0.12	0.14	0.19
trans									1	0.08	0.30
Cholesterol										1	0.64
Animal											1

[1] All correlations were significant.

RESULTS

During 10 y of follow-up (1991–2001), 860 women (6.4%) reported a first diagnosis of GDM. Correlations of energy-adjusted intakes of specific types of fat are presented in **Table 1**. Saturated fat intake was significantly correlated with intakes of *trans* fat ($r = 0.49$) and monounsaturated fat ($r = 0.76$). The intake of monounsaturated fat was correlated with intakes of *trans* fat ($r = 0.71$) and polyunsaturated fat ($r = 0.52$). At baseline, increasing quintiles of total fat, dietary cholesterol, and animal fat intakes were associated with a higher BMI, increased total meat and protein intakes, and decreased alcohol consumption and cereal fiber intake (**Tables 2** and **3**). Glycemic load, servings per day of fruit and vegetables, and the percentage of calories from carbohydrates were inversely associated with increasing quintiles of total fat, cholesterol intake, and intakes of animal and vegetable fats. Average daily total calories did not vary appreciably across increasing intakes of animal, vegetable, or total fat or cholesterol.

Higher intakes total fat, saturated fat, and *trans* fat were not significantly associated with GDM risk in fully adjusted models including both dietary and nondietary covariates (**Tables 4** and **5**). However, total fat was associated with significantly increased risk of GDM after adjustment for nondietary covariates that was no longer significant in the fully adjusted model, which was

TABLE 2
Baseline characteristics by quintiles of prepregnancy intakes of total fat and dietary cholesterol in 13,475 women

	Total fat (percentage of kcal)			Dietary cholesterol (mg)		
Baseline characteristics	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Cases	145	179	180	147	156	207
Age (y)	31.6 ± 3.4[1]	31.4 ± 3.3	31.4 ± 3.2	31.4 ± 3.3	31.5 ± 3.3	31.6 ± 3.3
Calories (kcal/d)	1823 ± 536	1837 ± 542	1792 ± 572	1797 ± 560	1860 ± 539	1778 ± 540
BMI (kg/m^2)	22.6 ± 3.7	23.5 ± 4.1	24.3 ± 5.1	22.7 ± 3.9	23.5 ± 4.2	24.3 ± 4.7
Alcohol intake (g/d)	3.3 ± 6.0	3.0 ± 4.9	2.6 ± 4.2	3.1 ± 5.4	3.1 ± 5.1	2.9 ± 4.6
Physical activity (MET-h/wk[2])	30.2 ± 35.5	21.5 ± 25.3	18.2 ± 23.6	27.6 ± 35.4	22.0 ± 26.1	21.4 ± 28.6
Glycemic load	146 ± 51	125 ± 42	102 ± 38	143 ± 53	126 ± 43	106 ± 38
Cereal fiber (g/d)	7.2 ± 5.2	5.9 ± 2.9	4.9 ± 2.6	7.1 ± 5.1	6.1 ± 3.2	5.1 ± 2.6
Red meat (servings/d)	0.31 ± 0.26	0.55 ± 0.34	0.76 ± 0.47	0.34 ± 0.27	0.57 ± 0.37	0.66 ± 0.46
Total meat (servings/d)	0.42 ± 0.34	0.79 ± 0.46	1.11 ± 0.68	0.48 ± 0.40	0.80 ± 0.52	0.94 ± 0.64
Fruit and vegetables (servings/d)	6.4 ± 3.4	4.9 ± 2.4	3.7 ± 2.0	5.5 ± 3.2	5.1 ± 2.7	4.7 ± 2.4
Protein intake (percentage of energy)	18.7 ± 3.7	19.4 ± 3.2	19.2 ± 3.1	16.3 ± 2.6	19.5 ± 2.6	21.9 ± 3.3
Carbohydrate intake (percentage of energy)	58.6 ± 5.9	49.8 ± 4.1	42.0 ± 4.6	57.7 ± 6.5	49.9 ± 5.3	44.5 ± 6.0
Family history of diabetes [*n* (%)]	367 (11.80)	307 (11.16)	311 (14.12)	312 (10.96)	341 (12.36)	297 (12.53)
Current smoker [*n* (%)]	216 (6.95)	239 (8.69)	279 (12.74)	222 (7.80)	266 (9.64)	242 (10.21)
Race [*n* (%)]						
African American	33 (1.06)	25 (0.91)	19 (0.87)	12 (0.42)	14 (0.51)	43 (1.81)
Hispanic	51 (1.64)	43 (1.56)	22 (1.00)	40 (1.40)	33 (1.20)	41 (1.73)
Asian	92 (2.96)	34 (1.24)	25 (1.14)	60 (2.11)	45 (1.63)	44 (1.86)
White	2890 (92.93)	2598 (94.44)	2075 (94.75)	2689 (94.45)	2613 (94.74)	2205 (93.00)
Other	44 (1.41)	51 (1.85)	49 (2.24)	46 (1.62)	53 (1.92)	38 (1.60)
Multivitamin use [*n* (%)]	1813 (58.30)	1457 (52.96)	982 (44.84)	1554 (54.58)	1463 (53.05)	1258 (53.06)
Nulliparous [*n* (%)]	1448 (47.95)	970 (36.56)	829 (38.90)	1320 (47.64)	1007 (37.57)	886 (38.50)

[1] Mean ± SD (all such values).
[2] MET-h/wk, metabolic equivalent task hours per week.

TABLE 3
Baseline characteristics by quintiles of prepregnancy animal and vegetable fat intakes in 13,475 women

Baseline characteristics	Animal fat (percentage of kcal)			Vegetable fat (percentage of kcal)		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Cases	125	167	230	200	172	144
Age (y)	31.8 ± 3.4[1]	31.4 ± 3.3	31.3 ± 3.1	31.4 ± 3.3	31.5 ± 3.3	31.6 ± 3.4
Calories (kcal/d)	1820 ± 559	1842 ± 534	1815 ± 556	1821 ± 537	1850 ± 542	1786 ± 566
BMI (kg/m^2)	22.5 ± 3.6	23.4 ± 4.1	24.3 ± 5.0	23.3 ± 4.1	23.4 ± 4.2	23.6 ± 4.6
Alcohol intake (g/d)	3.3 ± 5.6	3.0 ± 4.9	2.7 ± 4.6	3.0 ± 6.0	3.1 ± 5.0	2.9 ± 4.4
Physical activity (MET-h/wk[2])	30.5 ± 35.7	21.9 ± 27.0	18.8 ± 24.2	26.2 ± 32.6	22.2 ± 28.6	20.9 ± 25.8
Glycemic load	146 ± 52	126 ± 42	106 ± 39	131 ± 49	128 ± 46	115 ± 43
Cereal fiber (g/d)	7.6 ± 5.3	6.0 ± 3.0	4.8 ± 2.5	6.0 ± 3.7	6.3 ± 3.2	5.9 ± 3.1
Red meat (servings/d)	0.25 ± 0.20	0.53 ± 0.30	0.83 ± 0.47	0.53 ± 0.41	0.55 ± 0.38	0.48 ± 0.35
Total meat (servings/d)	0.34 ± 0.28	0.75 ± 0.41	1.19 ± 0.67	0.73 ± 0.56	0.78 ± 0.54	0.70 ± 0.51
Fruit and vegetables (servings/d)	6.3 ± 3.4	5.0 ± 2.6	4.1 ± 2.2	5.6 ± 3.0	5.0 ± 2.7	4.4 ± 2.6
Protein intake (percentage of energy)	17.3 ± 3.3	19.4 ± 3.0	20.8 ± 3.2	20.6 ± 3.7	19.1 ± 3.0	17.4 ± 2.8
Carbohydrate intake (percentage of energy)	58.4 ± 6.2	50.4 ± 4.5	43.0 ± 5.1	53.0 ± 7.9	50.5 ± 6.7	47.6 ± 6.5
Family history of diabetes [*n* (%)]	326 (11.57)	321 (11.53)	343 (13.25)	400 (12.67)	327 (11.62)	276 (13.06)
Current smoker [*n* (%)]	186 (6.60)	254 (9.13)	305 (11.79)	268 (8.49)	231 (8.21)	218 (10.31)
Race [*n* (%)]						
African American	19 (0.67)	20 (0.72)	36 (1.39)	42 (1.33)	25 (0.89)	11 (0.52)
Hispanic	51 (1.81)	31 (1.11)	36 (1.39)	47 (1.49)	34 (1.21)	27 (1.28)
Asian	86 (3.05)	32 (1.15)	34 (1.31)	83 (2.63)	38 (1.35)	37 (1.75)
White	2615 (92.83)	2655 (95.40)	2429 (93.86)	2945 (93.26)	2660 (94.56)	1991 (94.18)
Other	46 (1.63)	45 (1.62)	53 (2.05)	41 (1.30)	56 (1.99)	48 (2.27)
Multivitamin use [*n* (%)]	1569 (55.70)	1535 (55.16)	1283 (49.57)	1823 (57.73)	1491 (53.00)	1001 (47.35)
Nulliparous [*n* (%)]	1405 (50.98)	1040 (38.68)	860 (34.36)	1220 (39.87)	1081 (39.64)	897 (43.50)

[1] Mean ± SD (all such values).
[2] MET-h/wk, metabolic equivalent task hours per week.

adjusted for both dietary and nondietary covariates. The intake of animal fat was significantly and positively associated with GDM risk. Individuals in the highest quintile of animal fat intake had ~90% increased risk of GDM after adjustment for nondietary risk factors and vegetable fat intake (RR: 1.88; 95% CI: 1.36, 2.60) compared with that of individuals in the lowest quintile of intake. In addition, increased risk of highest compared with lowest quintiles of cholesterol intake was significantly associated with

TABLE 4
Prepregnancy total and source of dietary fat intakes and risk of gestational diabetes in 13,475 women[1]

Variable	Quintile					*P*-trend
	1	2	3	4	5	
Total fat (cases)	145	197	179	159	180	—
Median	48.30	56.40	61.85	67.30	75.05	—
RR1	1.0 (reference)[2]	1.32 (1.06, 1.64)	1.24 (0.99, 1.54)	1.15 (0.92, 1.45)	1.44 (1.15, 1.79)	0.01
RR2	1.0 (reference)	1.39 (1.11, 1.72)	1.35 (1.08, 1.68)	1.24 (0.99, 1.57)	1.45 (1.15,1.82)	0.01
RR3	1.0 (reference)	1.39 (1.10, 1.75)	1.36 (1.06, 1.76)	1.23 (0.93, 1.63)	1.36 (1.00, 1.85)	0.15
Source of fat models						
Animal fat (cases)	125	180	167	158	230	—
Median	24.35	30.40	34.30	38.60	44.80	—
RR1	1.0 (reference)	1.42 (1.12, 1.78)	1.24 (0.98, 1.57)	1.21 (0.95, 1.53)	1.71 (1.37, 2.14)	<0.0001
RR2	1.0 (reference)	1.50 (1.17, 1.90)	1.37 (1.08, 1.74)	1.35 (1.06. 1.72)	1.87 (1.49, 2.34)	<0.0001
RR3 and vegetable fat and *trans* fat	1.0 (reference)	1.55 (1.20, 1.98)	1.43 (1.09, 1.88)	1.40 (1.04, 1.89)	1.88 (1.36, 2.60)	0.05
Vegetable fat (cases)	200	178	172	166	144	—
Median	19.30	23.55	26.90	30.50	35.95	—
RR1	1.0 (reference)	0.95 (0.77, 1.16)	0.95 (0.77, 1.17)	1.02 (0.83, 1.26)	1.01 (0.82, 1.26)	0.72
RR2	1.0 (reference)	0.98 (0.79, 1.20)	0.96 (0.78, 1.19)	0.99 (0.80, 1.22)	0.96 (0.77, 1.20)	0.79
RR3 and animal fat and *trans* fat	1.0 (reference)	0.99 (0.80, 1.22)	1.00 (0.80, 1.26)	1.07 (0.84, 1.37)	1.15 (0.87, 1.51)	0.71

[1] Intakes were calculated as the percentage of energy by quintile as the cumulative updated average. Pooled logistic regression models were as follows: RR1, adjusted for age (5-y categories) and BMI (5 categories); RR2, additionally adjusted for parity, physical activity (metabolic equivalences/wk in 5 categories), family history of diabetes, smoking (never, past, or current), race, total energy intake (quintiles), and alcohol (quintiles of daily intake); and RR3, additionally adjusted for cereal fiber (quintiles), glycemic load (quintiles), dietary cholesterol (mg/d), and other fats listed in the table.
[2] RR; 95% CI in parentheses (all such values).

TABLE 5
Prepregnancy specific dietary fat and cholesterol intakes and risk of gestational diabetes in 13,475 women[1]

	Quintile					
Variables	1	2	3	4	5	*P*-trend
SFA (cases)	133	177	174	180	196	—
Median	16.15	19.40	21.67	24.00	27.55	—
RR1	1.0 (reference)[2]	1.26 (1.01, 1.58)	1.18 (0.94, 1.48)	1.19 (0.95, 1.49)	1.27 (1.02, 1.59)	0.10
RR2	1.0 (reference)	1.36 (1.08, 1.71)	1.27 (1.00, 1.60)	1.30 (1.03, 1.64)	1.34 (1.07, 1.69)	0.04
RR3 and *trans* fat, MUFA, and PUFA	1.0 (reference)	1.19 (0.92, 1.55)	1.01 (0.76, 1.36)	0.97 (0.71, 1.34)	0.89 (0.62, 1.28)	0.22
MUFA (cases)	145	182	186	174	173	—
Median	17.83	21.20	23.60	25.95	29.30	—
RR1	1.0 (reference)	1.24 (0.99, 1.54)	1.29 (1.04, 1.61)	1.32 (1.06, 1.65)	1.48 (1.18, 1.85)	0.0008
RR2	1.0 (reference)	1.30 (1.04, 1.63)	1.42 (1.13, 1.77)	1.41 (1.12, 1.76)	1.49 (1.18, 1.87)	0.0007
RR3 and SFA, PUFA, and *trans* fat	1.0 (reference)	1.22 (0.94, 1.59)	1.39 (1.03, 1.88)	1.43 (1.02, 2.03)	1.56 (1.04, 2.33)	0.04
PUFA (cases)	173	197	170	180	140	—
Median	8.13	9.50	10.60	11.80	13.80	—
RR1	1.0 (reference)	1.17 (0.95, 1.43)	1.12 (0.91, 1.39)	1.33 (1.08, 1.64)	1.20 (0.96, 1.50)	0.05
RR2	1.0 (reference)	1.17 (0.95, 1.44)	1.11 (0.90, 1.38)	1.33 (1.08, 1.65)	1.15 (0.92, 1.45)	0.11
RR3 and MUFA, SFA, and *trans* fat	1.0 (reference)	1.08 (0.87, 1.35)	1.00 (0.79, 1.26)	1.19 (0.93, 1.51)	1.01 (0.77, 1.32)	0.57
Trans unsaturated fat (cases)	153	169	180	186	172	—
Median	1.85	2.43	2.93	3.52	4.47	—
RR1	1.0 (reference)	1.12 (0.90, 1.40)	1.24 (0.99, 1.54)	1.27 (1.02, 1.57)	1.24 (0.99, 1.54)	0.02
RR2	1.0 (reference)	1.20 (0.96, 1.51)	1.32 (1.06, 1.65)	1.32 (1.06, 1.65)	1.25 (0.99, 1.57)	0.01
RR3 and MUFA, SFA, and PUFA	1.0 (reference)	1.08 (0.85, 1.37)	1.13 (0.88, 1.44)	1.09 (0.84, 1.41)	1.01 (0.76, 1.36)	0.37
PUFA:SFA ratio (cases)	216	191	170	161	122	—
Median	0.37	0.44	0.50	0.57	0.69	—
RR1	1.0 (reference)	0.96 (0.79, 1.17)	0.94 (0.77, 1.16)	1.03 (0.83, 1.26)	0.88 (0.71, 1.11)	0.44
RR2	1.0 (reference)	0.98 (0.80, 1.19)	0.93 (0.76, 1.14)	1.00 (0.81, 1.23)	0.84 (0.67, 1.06)	0.20
RR3 and *trans* fat and MUFA	1.0 (reference)	1.02 (0.83, 1.25)	0.99 (0.81, 1.23)	1.10 (0.88, 1.36)	0.98 (0.77, 1.25)	0.54
Cholesterol (cases)	147	165	156	185	207	—
Median (mg/d)	167	205	233	262	310	—
RR1	1.0 (reference)	1.06 (0.84, 1.32)	0.98 (0.78, 1.22)	1.21 (0.97, 1.50)	1.47 (1.18, 1.82)	<0.0001
RR2	1.0 (reference)	1.11 (0.88, 1.39)	1.02 (0.81, 1.29)	1.22 (0.98, 1.53)	1.50 (1.21, 1.87)	<0.0001
RR3 and MUFA, PUFA, SFA, and *trans* fat	1.0 (reference)	1.08 (0.86, 1.37)	1.01 (0.78, 1.29)	1.20 (0.93, 1.55)	1.45 (1.11, 1.89)	0.04
Omega-3 (cases)	203	159	182	155	161	—
Median	0.83	1.00	1.14	1.29	1.56	—
RR1	1.0 (reference)	0.84 (0.68, 1.03)	1.02 (0.84, 1.25)	0.93 (0.75, 1.15)	1.08 (0.88, 1.34)	0.28
RR2	1.0 (reference)	0.86 (0.69, 1.06)	1.04 (0.85, 1.28)	0.93 (0.75, 1.15)	1.04 (0.84, 1.29)	0.53
RR3 and *trans* fat, MUFA, SFA, and omega-6	1.0 (reference)	0.85 (0.68, 1.06)	1.03 (0.82, 1.29)	0.91 (0.71, 1.17)	1.03 (0.78, 1.36)	0.91
Omega-6 (cases)	193	175	166	187	139	—
Median	6.94	8.31	9.35	10.51	12.46	—
RR1	1.0 (reference)	0.88 (0.72, 1.09)	0.94 (0.76, 1.16)	1.15 (0.94, 1.41)	0.98 (0.79, 1.22)	0.43
RR2	1.0 (reference)	0.92 (0.75, 1.14)	0.98 (0.79, 1.21)	1.19 (0.97, 1.46)	0.98 (0.78, 1.22)	0.47
RR3 and *trans* fat, MUFA, SFA, and omega-3	1.0 (reference)	0.86 (0.69, 1.07)	0.87 (0.69, 1.11)	1.04 (0.80, 1.34)	0.82 (0.60, 1.12)	0.95

[1] Intakes were calculated as the percentage of energy by quintile as the cumulative updated average except cholesterol, which was calculated as the cumulative average of mg/d. Pooled logistic regression models were as follows: RR1, adjusted for age (5-y categories) and BMI (5 categories); RR2, additionally adjusted for parity, physical activity (metabolic equivalences/wk in 5 categories), family history of diabetes, smoking (never, past, or current), race, total energy intake (quintiles), and alcohol (quintiles of daily intake); and RR3, additionally adjusted for cereal fiber (quintiles), glycemic load (quintiles), and other fats as listed in the table.

[2] RR; 95% CI in parentheses (all such values).

GDM after adjustment for dietary and nondietary risk factors including specific fatty acids (RR: 1.45; 95% CI: 1.11, 1.89).

In this population, MUFA is a major component of animal fat, and the major source of animal fat is from red meat. In age- and BMI-adjusted analyses as well as models that were also adjusted for nondietary covariates, MUFA intake was significantly associated with GDM (*P*-linear trend = 0.008 and 0.007, respectively). In multivariate analyses that were also adjusted for dietary risk factors for GDM, including other specific fats, the association remained significant ($P = 0.04$).

TABLE 6
Multivariate RR of gestational diabetes associated with increases in 5% of energy from types of fat[1]

	Coefficient ± SE	RR each 5% increment of energy (95% CI)	*P*
Substitution for carbohydrate intake			
Model 1			
Animal fat	0.0204 ± 0.0042	1.13 (1.08, 1.18)	<0.0001
Vegetable fat	−0.0042 ± 0.0052	0.98 (0.93, 1.03)	0.42
Model 2			
Total fat	0.0080 ± 0.0048	1.04 (1.00, 1.08)	0.04
Substitution for animal fat intake			
Model 1			
Vegetable fat	−0.0148 ± 0.0059	0.93 (0.88, 0.98)	0.01

[1] Pooled logistic regression models were adjusted for period, age (5-y categories), BMI (quintiles), parity, protein (percentage of energy), physical activity, family history of diabetes, smoking, alcohol, total calories, cholesterol intake (mg/d), and race.

To further examine the association between dietary fat intakes and GDM, dietary fat exposures were modeled as continuous nutrient-density variables, which were simultaneously adjusted for each other and for other known risk factors (**Table 6**). These substitution models revealed results similar to the previous results. In the fully adjusted model, the replacement of 5% of energy from carbohydrates with animal fat increased risk of GDM by 13% (RR: 1.13; 95% CI: 1.08, 1.18). Similarly, the substitution of vegetable fat for animal fat suggested a decrease in risk of GDM (RR: 0.93; 95% CI: 0.88, 0.98; $P = 0.01$) for 5% of energy. The substitution of MUFA for carbohydrates (per each 5% of total calories) was associated with significantly increased risk of GDM (RR: 1.29; 95% CI: 1.09, 1.51; $P = 0.003$) (data not shown). No associations were observed between total omega-3 or total omega-6 fatty acids and risk of GDM.

Finally, we examined whether associations of total, specific, and source of fats differed according to major nondietary risk factors including current compared with noncurrent smoking, very physically active (fourth and fifth quintiles of activity, expressed in weekly metabolic equivalences) compared with less physical activity (first through third quintiles), a positive compared with negative family history of diabetes, BMI <25 compared with ≥ 25, or nulliparous compared with parous. No significant differences in associations between dietary fat intake and GDM risk by these factors were observed (all *P*-interactions were >0.05).

DISCUSSION

In this large, prospective cohort study of prepregnancy diet, we identified no significant association between total fat intake and GDM risk; however, we observed a significantly higher risk of GDM associated with greater consumption of dietary cholesterol and animal fat. Moreover, we estimated that the replacement of the percentage of total calories from carbohydrates with animal fat was associated with significantly increased risk of GDM, whereas the replacement of energy from animal fat with vegetable fat was suggestive of reduced risk.

Epidemiologic data that related prepregnancy dietary fat intake and GDM risk are sparse, and most studies on dietary fat intake during pregnancy were either small, retrospective, or provide insufficient control for dietary and nondietary potential confounding variables. We are aware of only 2 published studies on dietary cholesterol intakes and GDM risk (23, 24). Our observed association between a higher cholesterol intake and increased GDM risk was generally in line with findings from the 2 studies (23, 24). In a study of 41 GDM cases and 294 non-GDM controls, each increase in dietary cholesterol of 50 mg/1000 kcal during the previous year was associated with 88% increased risk of GDM (RR: 1.88; 95% CI: 1.09, 3.23) after adjustment for dietary and nondietary covariates (23). Moreover, >2-fold increased risk of GDM of the highest compared with lowest quintiles of cholesterol intake (3 mo before conception and during pregnancy) was observed in both a prospective and a retrospective analysis (24). In addition, results from the current study were consistent with those from other studies that documented positive associations of cholesterol intake with incident type 2 diabetes in men and nonpregnant women (25, 26), including in subjects within a similar cohort (ie, the Nurses' Health Study I) (27).

Although the precise mechanisms by which high dietary cholesterol consumption influences glucose homeostasis and diabetes risks are unclear, the observed association with GDM is biologically plausible. Overall, fatty acids play a vital role in glucose homeostasis (9), but dietary cholesterol specifically may have a unique role in β cell dysfunction, which is a necessary step in the development of GDM. Animal models have shown that cholesterol accumulation in islets contributes to glucose intolerance that can lead to β cell dysfunction (28). Furthermore, although human data are sparse, the variation in genes involved in cholesterol metabolism, such as ABCA1 have been associated with type 2 diabetes risk (29). ABCA1 regulates the excretion of cholesterol from β cells, and in the absence of ABCA1, the islet cell cholesterol content increases and impairs insulin secretion (29). Additional research is warranted to determine the exact mechanism by which cellular cholesterol may be associated with impaired pancreatic β cells.

We also observed that a high intake of animal fat was associated with increased risk of GDM. Although we are unaware of previous studies that specifically evaluated prepregnancy animal fat intake and risk of GDM, the intake of animal fat was previously shown to be associated with type 2 diabetes in women with a history of GDM (30). The intake of animal fat was highly correlated with intakes of several nutrients and food sources of nutrients that were related to elevated risk of GDM. For example, meat products are a primary source of MUFAs and the consumption of MUFA and animal fat were highly correlated in this

cohort ($r = 0.85$), and an association between MUFA and GDM may partially explain the association between animal fat and GDM.

The replacement of energy from carbohydrates for energy from MUFA was associated with increased risk of GDM even after adjustment for saturated fat and dietary cholesterol, which are other components of animal fat that may increase risk of GDM. The association of MUFA with GDM risk was consistent with observational analyses that relating MUFA intake and type 2 diabetes in nonpregnant women (27). However, this association conflicted with findings from clinical trials. For example, compared with diets rich in saturated fats, diets high in MUFA appear to improve insulin sensitivity; however, the protective effect does not hold for diets high in total fat (>38%) (31). However, in difference from the clinical trial and some other studies, the major source of MUFA in the current study population was from animal fat, which is also the main source for saturated fat. Additional studies are necessary to determine the independent effects of MUFA and other components of animal fat on GDM risk.

In the current study, no significant associations of PUFA, saturated fat, the ratio of PUFA to saturated fat, or *trans* fat intakes with GDM risk were observed. Epidemiologic data provided consistent evidence for an inverse association between type 2 diabetes risk and PUFA or the ratio of PUFA to saturated fat intakes as well as a positive association with dietary *trans* fat and saturated fat (32). However, the findings on the relation of these fatty acids with GDM are less consistent. Similar to our findings, 4 studies failed to find any association between PUFA intake and GDM risk (15, 23, 33) or recurrence (14). By contrast, increased risk of GDM was associated with a decreased intake of PUFA in several other studies (12, 16, 17). Similarly, intakes of dietary saturated fat were positively associated with GDM risk in some studies (16, 17, 34) but not in other studies (12, 13, 15, 23). Differences in study design, measurement methods of dietary fatty acids, and adjustment for other dietary factors may have accounted, at least in part, for the different findings across studies.

Several strengths of the current study served to minimize sources of measurement error and bias. These included the large sample size that far exceeded previous analyses of dietary fat and GDM, the prospective study design, repeated dietary assessments, a high rate of follow-up, and more importantly, the availability of comprehensive information on dietary and nondietary covariates. However, several potential limitations merit discussion. Because of the observational nature of the study, we could not rule out the possibility of unmeasured and unknown confounders that might have led to residual confounding. However, the association persisted after we adjusted for major dietary and nondietary risk factors of GDM. As in other observational studies, dietary data measured by FFQs are subject to measurement error; however, because of the prospective design, misclassification was likely to be nondifferential, which was likely to bias results toward the null. In addition, the FFQ has been validated, and the 3 repeated assessments over 8 y of follow-up helped reduce the extent of this error. Lastly, dietary intakes specifically during pregnancy were not measured in the current study. However, available limited data indicated that energy-adjusted macronutrient intakes, including of animal fat, were highly correlated with those in the second trimester of pregnancy (13), although women generally increased their caloric intake in pregnancy to meet fetal needs. Additional studies are needed to examine associations of dietary fat before and during pregnancy with GDM risk.

In conclusion, findings from this large prospective study suggest that, although the overall intake of prepregnancy dietary fat was not associated with risk of GDM, intakes of dietary cholesterol and animal fat were related to elevated risk independent of other major dietary and nondietary risk factors of GDM. More research to confirm these findings and to decipher underlying molecular mechanisms is warranted. However, these findings underline the potential importance of considering the fatty acid content of diet in dietary recommendations for the prevention of GDM.

The authors' responsibilities were as follows—KB, DKT, FBH, and CZ: designed the research; KB and DKT: conducted the research and analyzed data; KB and CZ: wrote and revised the manuscript and had primary responsibility for the final content of the manuscript; and all authors: critically read the manuscript, provided feedback, and read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES

1. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care 2004;27:S88–90.
2. Buchanan TA, Xiang A, Kjos S, Watanabe R. What is gestational diabetes? Diabetes Care 2007;30:S105–S111.
3. Zhang C, Liu S, Solomon C, Hu F. Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. Diabetes Care 2006;29:2223–30.
4. Zhang C. A prospective study of dietary patterns, meat intake and the risk of gestational diabetes mellitus. Diabetologia 2006;49:2604–13.
5. Tobias DK, Zhang C, van Dam RM, Bowers K, Hu FB. Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis. Diabetes Care 2011;34:223–9.
6. Chen L, Hu FB, Yeung E, Willett W, Zhang C. Prospective study of pre-gravid sugar-sweetened beverage consumption and the risk of gestational diabetes mellitus. Diabetes Care 2009;32:2236–41.
7. Bowers K, Yeung E, Williams MA, Qi L, Tobias DK, Hu FB, Zhang C. A prospective study of pre-pregnancy dietary iron intake and risk for gestational diabetes. Diabetes Care 2011;34:1557–63.
8. Boden G, Chen X, Ruiz J, White JV, Rossetti L. Mechanisms of fatty acid-induced inhibition of glucose uptake. J Clin Invest 1994;93:2438–46.
9. Storlien LH, Pan DA, Kriketos AD, O'Connor J, Caterson ID, Cooney GJ, Jenkins AB, Baur LA. Skeletal muscle membrane lipids and insulin resistance. Lipids 1996;31(suppl):S261–5.
10. Clarke SD. The multi-dimensional regulation of gene expression by fatty acids: polyunsaturated fats as nutrient sensors. Curr Opin Lipidol 2004;15:13–8.
11. Poitout V, Amyot J, Semache M, Zarrouki B, Hagman D, Fontés G. Glucolipotoxicity of the pancreatic beta cell. Biochim Biophys Acta 2010;1801:289–98.
12. Wang Y. Dietary variables and glucose tolerance in pregnancy. Diabetes Care 2000;23:460–4.
13. Radesky JS, Oken E, Rifas-Shiman SL, Kleinman KP, Rich-Edwards JW, Gillman MW. Diet during early pregnancy and development of gestational diabetes. Paediatr Perinat Epidemiol 2008;22:47–59.
14. Moses RG. The recurrence of gestational diabetes: could dietary differences in fat intake be an explanation? Diabetes Care 1997;20:1647–50.
15. Saldana TM, Siega-Riz A, Adair L. Effect of macronutrient intake on the development of glucose intolerance during pregnancy. Am J Clin Nutr 2004;79:479–86.
16. Bo S. Dietary fat and gestational hyperglycaemia. Diabetologia 2001; 44:972–8.
17. Chen X, Scholl TO, Leskiw M, Savaille J, Stein TP. Differences in maternal circulating fatty acid composition and dietary fat intake in women with gestational diabetes mellitus or mild gestational hyperglycemia. Diabetes Care 2010;33:2049–54.

18. Solomon CG, Willett W, Carey V, Rich-Edwards J, Hunter D, Colditz G, Stampfer M, Speizer F, Spiegelman D, Manson J. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA 1997;278:1078–83.
19. Agricultural Research Service. USDA Nutrient Database for Standard Reference. Release 10. Washington, DC: USDA, 1995.
20. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–99.
21. Willett W, Hennekens CH, Castelli W, Rosner B, Evans D, Taylor J, Kass EH. Effects of cigarette smoking on fasting triglyceride, total cholesterol, and HDL-cholesterol in women. Am Heart J 1983;105:417–21.
22. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. 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;149:531–40.
23. González-Clemente JM, Carro O, Gallach I, Vioque J, Humanes A, Sauret C, Abella M, Gimenez-Perez G, Mauricio D. Increased cholesterol intake in women with gestational diabetes mellitus. Diabetes Metab 2007;33:25–9.
24. Qiu C, Frederick IO, Zhang C, Sorensen TK, Enquobahrie DA, Williams MA. Risk of gestational diabetes mellitus in relation to maternal egg and cholesterol intake. Am J Epidemiol 2011;173:649–58.
25. Meyer KA, Kushi LH, Jacobs DR Jr, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. Diabetes Care 2001;24:1528–35.
26. Feskens EJ, Virtanen SM, Rasanen L, Tuomilehto J, Stengard J, Pekkanen J, Nissinen A, Kromhout D. Dietary factors determining diabetes and impaired glucose tolerance. A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetes Care 1995;18:1104–12.
27. Salmerón J, Hu F, Manson J, Stampfer M, Colditz G, Rimm E, Willett W. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019–26.
28. Brunham LR, Kruit JK, Pape TD, Timmins JM, Reuwer AQ, Vasanji Z, Marsh BJ, Rodrigues B, Johnson JD, Parks JS, et al. Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment. Nat Med 2007;13:340–7.
29. Brunham LR, Kruit JK, Verchere CB, Hayden MR. Cholesterol in islet dysfunction and type 2 diabetes. J Clin Invest 2008;118:403–8.
30. Kim SH, Kim MY, Yang JH, Park SY, Yim CH, Han KO, Yoon HK, Park S. Nutritional risk factors of early development of postpartum prediabetes and diabetes in women with gestational diabetes mellitus. Nutrition 2011;27:782–8.
31. Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nalsen C, Berglund L, Louheranta A, Rasmussen BM, et al. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU Study. Diabetologia 2001;44:312–9.
32. Risérus U, Willett W, Hu F. Dietary fats and prevention of type 2 diabetes. Prog Lipid Res 2009;48:44–51.
33. Tovar A, Must A, Bermudez OI, Hyatt RR, Chasan-Taber L. The impact of gestational weight gain and diet on abnormal glucose tolerance during pregnancy in Hispanic women. Matern Child Health J 2009;13:520–30.
34. Ying H, Wang D. Effects of dietary fat on onset of gestational diabetes mellitus. Zhonghua Fu Chan Ke Za Zhi 2006;41:729–31.