Healthful Dietary Patterns and Type 2 Diabetes Mellitus Risk Among Women With a History of Gestational Diabetes Mellitus

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Background: Type 2 diabetes mellitus (T2DM) has reached epidemic proportions. Women with gestational diabetes mellitus (GDM) are at high risk for T2DM after pregnancy. Adherence to healthful dietary patterns has been inversely associated with T2DM in the general population; however, whether these dietary patterns are associated with progression to T2DM among a susceptible population is unknown.

Methods: Four thousand four hundred thirteen participants from the Nurses’ Health Study II cohort with prior GDM were followed up from 1991 to 2005. We derived the alternate Mediterranean diet (aMED), Dietary Approaches to Stop Hypertension (DASH), and alternate Healthy Eating Index (aHEI) dietary pattern adherence scores from a post-GDM validated food-frequency questionnaire, with cumulative average updating every 4 years. Multivariable Cox proportional hazards models estimated the relative risk (hazard ratios) and 95% confidence intervals.

Results: We observed 491 cases of incident T2DM during 52,743 person-years. All 3 patterns were inversely associated with T2DM risk with adjustment for age, total calorie intake, age at first birth, parity, ethnicity, parental diabetes, oral contraceptive use, menopause, and smoking. When we compared participants with the highest adherence (quartile 4) vs lowest (quartile 1), the aMED pattern was associated with 40% lower risk of T2DM (hazard ratio, 0.60 [95% CI, 0.44-0.82; P=.002]); the DASH pattern, with 46% lower risk (0.54 [0.39-0.73; P<.001]); and the aHEI pattern, with 57% lower risk (0.43 [0.31-0.59; P<.001]). Adjustment for body mass index moderately attenuated these findings.

Conclusions: Adherence to healthful dietary patterns is associated with lower T2DM risk among women with a history of GDM. The inverse associations are partly mediated by body mass index.


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crucial for postpartum and lifelong dietary modifications to prevent T2DM.

METHODS

STUDY POPULATION

The study population consists of women with a history of GDM in the Nurses’ Health Study II, an ongoing prospective cohort established in 1989 with the enrollment of 166,671 female nurses, ages 24 to 44 years at baseline. Questionnaires are distributed every 2 years to update lifestyle and medical characteristics and to capture incident health outcomes. Follow-up for each questionnaire cycle is greater than 90%. This study has been approved by the institutional review board of the Partners HealthCare System, Boston, Massachusetts, with the participants’ consent implied by the return of the questionnaires.

Participants were eligible if they reported a history of GDM at baseline (1991). Women also became eligible during follow-up if they reported incident GDM at any time through the 2001 questionnaire because the update of GDM occurrence ceased after 2001. Gestational diabetes mellitus was assessed via self-report of a physician’s diagnosis, which has been previously validated against medical records (94% confirmed) in a subgroup of this population. Participants were restricted from analysis if they reported chronic disease (eg, T2DM, a cardiovascular disease event, or cancer) at baseline, before their GDM pregnancy, or before the return of their first post-GDM food frequency questionnaire (FFQ) or if they had a multiple-birth pregnancy, missing dietary exposure information, more than 70 FFQ items left blank, or unrealistic reports of total energy intake (<500 or >3500 kcal/d).

EXPOSURE ASSESSMENT

In 1991 and every 4 years thereafter, participants completed a semiquantitative FFQ. The FFQ captured usual intake of several common food items during the past year and has been extensively validated. Three dietary pattern adherence scores (the aMED, DASH, and aHEI) were computed for each FFQ cycle after the first reported GDM pregnancy. Scoring methods and justification for inclusion of the components have been described in detail elsewhere. Total scores consisted of the sum of points earned across all dietary components, with a higher score indicating greater adherence, ranging from 0 to 8 for the aMED, 8 to 39 for the DASH, and 2.5 to 87.5 for the aHEI. Briefly, to derive the aMED score, participants were assigned 1 point for being above the median number of servings per day for the following components: fruit, vegetables, legumes and soy, nuts, fish and seafood, whole grains, and the ratio of monounsaturated to saturated fatty acids (MUFA:SFA), Red and processed meat was scored 1 point for being below the median intake, and moderate alcohol intake (3-15 g/d) was scored 1 point. We conducted a sensitivity analysis removing the MUFA:SFA, because the primary source of MUFA in Western diets (beef and dairy) differs from the traditional Mediterranean diets (plant-based oils). To derive the DASH score, women were assigned 1 to 5 points based on their quintile of intake (servings per day) of fruit, vegetables, nuts, legumes and soy, red and processed meats, whole grains, low-fat dairy, and sodium (in milligrams). Sweetened beverages were derived from quartiles of usual intake owing to less variability. Scoring was reversed for red and processed meats, sugar-sweetened beverages, and sodium, with more points for less consumption. For the aHEI score, points were allotted for intake of each component on a scale from 0 to 10, with 10 indicating adherence to the recommended levels of servings per day and 0, the worst intake. Intermediate scores were categorized proportionately for fruit, vegetables, nuts and soy, the ratio of white to dark meat, cereal fiber (in grams), alcohol, the ratio of polyunsaturated fatty acids to SFA (in grams), and trans fat (percentage of total energy). Multivitamin use was scored as 2.5 points for 0 to 4 years of use and 7.5 points for 5 or more years of use.

OUTCOME ASSESSMENT

Participants reporting a physician’s diagnosis of T2DM were mailed a supplemental questionnaire. Confirmed cases were defined from this additional information according to the National Diabetes Data Group classification as those reporting at least 1 of the following: 1 or more classic symptoms (ie, excessive thirst, polyuria, unintentional weight loss, and hunger) and a fasting plasma glucose concentration of 140 mg/dL or more (to convert glucose levels to millimoles per liter, multiply by 0.0555) or a random plasma glucose level of 200 mg/dL or more; no symptoms but 2 or more elevated plasma glucose concentrations on more than 1 occasion (fasting level, ≥140 mg/dL; random level, ≥200 mg/dL); 2-hour oral glucose tolerance test finding, ≥200 mg/dL); or use of hypoglycemic medication (insulin or an oral hypoglycemic agent). Diagnostic criteria were changed in June 1998 to adopt a new diagnostic threshold for a fasting plasma glucose level of more than 126 mg/dL. A subgroup validation study conducted in a similar cohort of US female nurses found high accuracy (98%) comparing our classification against medical records.

COVARIABLE ASSESSMENT

Age was computed from the date of birth to the date of questionnaire return for each risk set. Body mass index (BMI), calculated as self-reported weight in kilograms divided by self-reported height in meters squared, was highly correlated with measured weight among a random subset of Boston-area cohort participants (r = 0.97). Total physical activity was ascertained by the frequency of engaging in common recreational activities, from which metabolic equivalent task–hours per week were derived. The questionnaire-based estimates correlated well with detailed activity diaries in a prior validation study (r = 0.56). Other relevant covariates captured on the biennial questionnaires included age at first birth, oral contraceptive use, months of breastfeeding, menopausal status, smoking status, self-reported race and ethnicity, and parental history of hypertension and diabetes. Parity was defined as the number of pregnancies lasting longer than 6 months.

STATISTICAL ANALYSIS

Baseline characteristics were derived from the questionnaire period in which participants first reported a GDM pregnancy. Dietary pattern adherence scores were updated as the cumulative average of all scores since GDM to reduce random within-person error and to represent long-term usual intake. Updating ceased if a participant reported incident chronic disease (eg, cardiovascular disease or cancer) to reduce reverse causation. Missing exposure data were carried forward from the most recent post-GDM FFQ for which data were captured. Follow-up time was computed from the date of GDM diagnosis to the date of T2DM diagnosis, death, or return of the 2005 questionnaire, whichever came first. We computed pairwise Pearson correlations between scores to assess overlap of the exposures. We used Cox proportional hazards models stratified by time since the GDM diagnosis to estimate the relative risks (hazard ratio [HR]) and 95% confidence intervals for associations be-
tween dietary pattern adherence and risk of incident T2DM. Scores were analyzed continuously for a 1-unit increase in adherence in the interquartile range (IQR) and categorically in quartiles, with the lowest adherence (quartile 1) as the reference group. We computed χ² tests for trend across quartiles by modeling the median scores of each quartile as a continuous variable. Our first multivariable model adjusted for age and total energy intake. Additional multivariable models further adjusted for possible confounders, including parity, age at first birth, race and ethnicity, parental history of diabetes, oral contraceptive use, menopausal status, smoking status, physical activity, and, subsequently, BMI. Alcohol intake was also included in the DASH models because intake was not a component of the score and is a potential lifestyle confounder. We included BMI in the model separately because BMI is also a plausible intermediate between exposure and outcome. The proportion of the associations mediated by BMI was estimated with a macro developed by Donna Spiegelman, ScD, and colleagues (Mediate SAS; Harvard School of Public Health; available at http://www.hsph.harvard.edu/faculty/donna-spiegelman/software/mediate/). This macro computes the magnitude of mediation, the 95% confidence interval, and the P value for significance.25 Time-varying lifestyle covariates were updated biennially. Categorical covariates included an indicator variable for missing data, if necessary.

Secondary analyses assessed effect modification by overweight status (BMI, <25.0 vs ≥25.0), age (<35 vs ≥35 years), parental history of diabetes (none vs either parent), and physical activity (metabolic equivalent task-hours per week, ≤15.4 vs ≥15.5). We derived P values for heterogeneity from 1 df −2 log likelihood ratio test χ² statistics, comparing the main effects model with and without the addition of the multiplicative interaction terms.

We also analyzed each pattern’s components, modeling all components simultaneously to assess a 1-point increase in total score by a given dietary factor. This analysis assessed whether the contribution of any individual component or components explained the association observed between total scores and diabetes risk. In an additional sensitivity analysis to address the potential for screening bias, we restricted cases to those reporting at least 1 classic diabetic symptom at the time of diagnosis. We used commercially available software (SAS, version 9.1; SAS Institute, Inc).

RESULTS

Baseline characteristics of the participants are given in Table 1 and Table 2. Overall, 4413 participants with a history of GDM met our inclusion criteria, contributing 52,743 person-years of observation. On average, participants in quartile 4 (highest adherence) of each pattern score had a lower BMI, consumed more alcohol, consumed more total calories from carbohydrates and less from animal fat, were less likely to be current smokers, and were less likely to have a parental history of diabetes (Tables 1 and 2). The dietary pattern adherence scores were significantly correlated with one another (P < .001). During 16 years of observation, 491 participants (11.1%) developed T2DM. Mean time from GDM to development of T2DM was 13.8 (median, 13.5; range, 2.0-27.6) years. Mean age at diagnosis of T2DM was 46.5 (median, 46.7; range, 32.4-59.8) years.

All 3 dietary pattern adherence scores were strongly and inversely associated with T2DM risk after adjusting for age and total energy intake (model 1) (Table 3 and eTable [http://www.archinternmed.com]). Adjustment for other confounders (model 2) did not substantially change the findings; however, adjustment for BMI (model 3) partially attenuated the effect estimates for all 3 dietary patterns. Breastfeeding did not affect results. Independent of BMI, a 1-unit IQR increase in score adherence to the aMED dietary pattern was associated with a 15% lower risk for T2DM (IQR, 3.0-5.0; HR, 0.84 [95% CI, 0.73-0.96; P = .001]); in the DASH, a 10% lower risk...
and in the aHEI, a 17% lower risk (IQR, 30.5-45.5; HR, 0.77 [0.64-0.93]; P = .007). Body mass index was estimated to mediate 41% (95% CI, 19%-63%; P < .001) of the association between aMED pattern adherence and T2DM risk; 39% (15%-64%; P = .002), between the DASH pattern and T2DM risk; and 50% (28%-72%; P < .001), between the aHEI pattern and T2DM risk.

Tests for heterogeneity did not suggest effect modification by parental history of diabetes, age, BMI, or physical activity level for all 3 dietary patterns. When we assessed the association between a 1-point increase by an individual pattern component in the multivariable model, including all other components simultaneously, several factors within the dietary patterns trended toward an inverse association with incident T2DM. For the aMED pat-
tern, this trend included vegetable intake, fish and seafood intake, and moderate alcohol consumption. For the DASH pattern, vegetable intake, less intake of red and processed meat, and decreased intake of sugar-sweetened beverages were inverse. For the aHEI pattern, the trend included vegetable intake, an increased ratio of white to dark meat, an increased intake of cereal fiber, moderate alcohol consumption, and long-term multivitamin use. In addition, removing MUFA:SFA from the aMED score produced similar results, and inclusion of only symptomatic T2DM cases gave similar effect estimates, although statistical power was reduced.

**COMMENT**

In this large prospective cohort of 4413 women with a history of GDM, we found that adherence to healthful dietary patterns, in particular the aHEI, is inversely associated with progression to T2DM. The significant association persisted even after the adjustment of other risk factors for T2DM.

We did not perform direct comparisons of dietary patterns for several reasons. First, we used previously published scoring methods to estimate adherence to each of the patterns, which produced substantially different scales; thus, differences in the precision of exposure measurement may partially explain differences in the observed effect estimates. Second, all scores were significantly and inversely associated with T2DM risk, with broadly overlapping 95% confidence intervals. Analyses to detect minor differences might therefore be statistically underpowered. Finally, the dietary patterns shared several common components, suggesting that, in general, an overall healthful dietary pattern may be beneficial for the prevention of T2DM.

Our findings are consistent with previous findings between diet and T2DM in the general population, however, we are unaware of previous studies investigating healthful dietary patterns and T2DM risk among the high-risk population of women with a history of GDM. The recent Diabetes Prevention Program clinical trial enrolled individuals with impaired glucose tolerance at baseline, including 350 women with a history of GDM. The GDM participants in the intensive lifestyle intervention (diet and physical activity advice) experienced a reduced risk for T2DM compared with the standard lifestyle and placebo intervention (53% vs 49%). Inference from that intervention study was limited by the relatively small sample size (350 GDM cases and 122 T2DM cases). Moreover, the intervention effect was not specific to dietary modifications only.

Plausible biological mechanisms may explain the observed associations between healthful dietary patterns and the delay or prevention of progression of GDM to T2DM. Evidence suggests that women with prior GDM have diminished beta cell function. Thus, factors that increase insulin sensitivity may minimize beta cell compensation, preserving their capacity over time. Carbohydrate quality, intake of vegetables and fruit, lower intake of red and processed meats, and low intake of SFA are common characteristics between the dietary patterns included in this analysis. Carbohydrate quality, reflected by intake of whole grains and cereal fiber, may mitigate beta cell demands by blunting intestinal glucose absorption and downstream insulin burden. Glycemic index and glyceremic load are measures of this rise in insulin levels after glucose uptake and have been associated with chronic hyperglycemia and hyperinsulinemia. Vegetables and fruit are high in micronutrients such as magnesium, antioxidants such as vitamins C and E, phytochemicals, and fiber, leading to reductions in free radical–induced oxidative stress, a condition correlated with pancreatic tissue damage. Fish and seafood intake was inversely associated with T2DM risk as a component of the aMED dietary pattern in our study and was a source of ω-3 polyunsaturated fatty acids, vitamin D, protein, and selenium. Current evidence between polyunsaturated fatty acids and T2DM risk is mixed. Inverse associations in the observational literature largely have not been supported by short-term trials of fatty acid supplementation and markers of insulin resistance, thus, which elements of seafood might benefit T2DM risk remain unclear.

Increases in healthful dietary factors may also incur a benefit by replacing harmful food options. For example, substitution of red meat servings with several other foods (nuts, fish, whole grains, and poultry) was associated with lower T2DM risk in a previous analysis conducted among initially healthy women. Constituents of red and processed meat include heme iron, a pro-oxidant that may lead to increased oxidative stress and damage similar to that described in the preceding paragraph. Nitrosamines in processed red meats are created during digestion and with certain cooking methods and have been associated with insulin resistance, decreased insulin secretion, and diabetes in animal studies. Finally, the mechanism by which moderate alcohol consumption may prevent diabetes is unclear, although consumption has been associated with improved insulin sensitivity and high-density lipoprotein cholesterol concentration and with suppressed gluconeogenesis.

Although several macronutrients, micronutrients, and individual foods have been associated with diabetes risk, assessment of dietary patterns offers a comprehensive and complementary approach of the association between diet and disease. In addition, dietary patterns may be more applicable to public health interventions because people tend to consume complex and diverse meals rather than individual components in isolation. Analyzing food patterns also accounts for any interactions or synergistic effects between individual foods or nutrients. Other strengths of this analysis include our adjustment for several confounding lifestyle factors. With the exception of BMI, changes in the effect estimates after adjustment for several well-known diabetes risk factors were minimal; thus, it seems unlikely that unmeasured or residual confounding would account for the observed associations. Exposure assessment by validated FFQ was an additional strength of this analysis, and cumulative update of repeated exposure measures reduced misclassification from random within-person error and better represented long-term intake. Long-term prospective follow-up eliminated recall bias and allowed us to observe
participants from GDM exposure to incident T2DM. With almost 500 cases, the study had adequate statistical power.

This analysis has some limitations. First, because most of our study population consisted of white Americans, we cannot ascertain whether our findings are similar across other race and ethnic groups. However, the relative homogeneity of our population advantageously reduces potential sources of unmeasured confounding. Second, screening bias may result if more health-conscious women regularly visit a physician, thus increasing their chance of receiving a medical diagnosis. Similar results were seen when we restricted cases to symptomatic T2DM, minimizing concerns for this bias.

In summary, we observed significant inverse associations between increased adherence to the aMED, DASH, and aHEI dietary patterns and incident T2DM in this large prospective study of women at high risk with a history of GDM and long-term follow-up. Identifying postpartum modifiable risk factors and increasing education are crucial for the early prevention of T2DM among this high-risk population. Findings from the present study suggest that public health efforts targeting women with a history of GDM for the prevention of T2DM may consider encouraging diets rich in whole grains, fruit, vegetables, and protein sources such as white meat, seafood, nuts, and legumes and reducing intake of red and processed meats and sugar-sweetened beverages.

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Author Contributions: Dr Tobias had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tobias, Hu, and Zhang. Acquisition of data: Hu. Analysis and interpretation of data: Tobias, Chavarro, Rosner, and Mozaffarian. Drafting of the manuscript: Tobias and Zhang. Critical revision of the manuscript for important intellectual content: Hu, Chavarro, Rosner, Mozaffarian, and Zhang. Statistical analysis: Tobias, Chavarro, and Rosner. Administrative, technical, and material support: Tobias. Study supervision: Hu, Mozaffarian, and Zhang.

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Online-Only Material: The eTable is available at http://www.archinternmed.com.

REFERENCES