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## Diet during early pregnancy and development of gestational diabetes

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### Summary

Diet composition may be a modifiable predictor of risk for abnormal glucose tolerance during pregnancy. Prior studies suggest that diets high in total fat, saturated fat, red and processed meats, and with high glycaemic load increase the risk of developing gestational diabetes mellitus (GDM), while polyunsaturated fats, carbohydrates and fibre are protective. The aim of this study was to investigate associations of these and other nutrients and foods, including n-3 fatty acids, *trans* fats, whole grains and dietary patterns, with risk of GDM. We studied 1733 women with singleton pregnancies enrolled in Project Viva, a prospective pregnancy and birth cohort study in eastern MA. Using multinomial logistic regression, we examined associations of first trimester diet, assessed by validated food frequency questionnaire, with results of glucose tolerance testing at 26–28 weeks of gestation.

A total of 91 women developed GDM and 206 women had impaired glucose tolerance (IGT). Pre-pregnancy body mass index (BMI) was a strong predictor for GDM risk (OR 3.44 [95% CI 1.88, 6.31] for pre-pregnancy BMI  $\geq 30$  vs.  $< 25$  kg/m<sup>2</sup>). After adjustment for confounders, the OR [95% CI] for risk of GDM for total dietary fat was 1.00 [0.96, 1.05], for saturated fat 0.98 [0.88, 1.08], for polyunsaturated fat 1.09 [0.94, 1.26], for *trans* fat 0.87 [0.51, 1.49], and for carbohydrates 1.00 [0.96, 1.03] per each 1% of total energy. The adjusted OR [95% CI] for risk of GDM for a one standard deviation increase in energy-adjusted glycaemic load (32 units, about two soft drinks) was 0.96 [0.76, 1.22] and for each daily serving of whole grains was 0.90 [0.73, 1.13]. Dietary patterns and intake of red and processed meats were not predictive of glucose tolerance outcome. Estimates for IGT were similar to those for GDM. Intake of n-3 fatty acids was associated with increased GDM risk (OR 1.11 [95% CI 1.02, 1.22] per each 300 mg/day), but not with IGT risk. Except for this finding, perhaps due to chance, these data do not show that nutrient or food intake in early pregnancy is linked to risk of GDM. Nutritional status entering pregnancy, as reflected by pre-pregnancy BMI, is probably more important than pregnancy diet in development of GDM.

### Keywords

gestational diabetes; impaired glucose tolerance; maternal pre-pregnancy BMI; maternal diet; omega-3 fatty acids

## Introduction

Gestational diabetes mellitus (GDM), diabetes first diagnosed during pregnancy, has an incidence of 2–5%<sup>1</sup> and is associated with poor pregnancy outcomes<sup>2</sup> as well as increased risk of longer-term morbidity for both mother and child.<sup>3</sup> Milder degrees of impaired glucose tolerance (IGT) may confer many of the same risks.<sup>4</sup> The prevalence of GDM in the United States has increased in the last decade,<sup>5–7</sup> hence the need for novel preventive strategies.

Identified ‘modifiable’ risk factors for GDM, including pre-pregnancy body mass index (BMI, kg/m<sup>2</sup>), exercise habits, and smoking<sup>8–10</sup> may be difficult to change. Recently, a handful of studies have examined diet quality during pregnancy as a potentially modifiable contributor to GDM risk.<sup>11–16</sup> Earlier studies, many of which were cross-sectional or retrospective in design, suggested that macronutrient makeup of the diet in mid-pregnancy may predict incidence<sup>11, 13,14</sup> or recurrence<sup>12</sup> of GDM. In particular, Saldana and colleagues<sup>14</sup> showed that higher intake of fat and lower intake of carbohydrates may be associated with increased risk of GDM and IGT. High fibre intake, which has been consistently linked to decreased risk of type 2 diabetes mellitus (DM) among non-pregnant adults,<sup>17–22</sup> was related to lower risk of GDM in two studies,<sup>12,16</sup> but not in others.<sup>11,13</sup> More recently, high dietary glycaemic load, also shown to be associated with increased DM risk in several non-pregnant cohorts,<sup>17–19</sup> was associated with the development of GDM in a large prospective study.<sup>16</sup>

Intake of specific types of dietary fat has also been implicated in GDM risk, with evidence from case-control studies that polyunsaturated fat may be protective against GDM and IGT,<sup>13</sup> and high intake of saturated fat detrimental.<sup>11</sup> However, these analyses did not adjust one type of fat for others, which is important as intake of different fat subtypes tends to be correlated and may have opposing effects.<sup>23</sup> In addition to these nutrient-specific analyses, recent work has examined food groups and dietary patterns with regard to glucose tolerance in pregnancy, finding that GDM was predicted by high intake of red and processed meats and a Western type dietary pattern (i.e. high in red meat, refined sugars, and fried or snack foods).<sup>15</sup>

An extensive body of literature has reported on associations of a number of other dietary factors with the development of DM among adult men and non-pregnant women. This literature suggests that total carbohydrate and fat intake are not related to DM risk, but specific types of carbohydrates, e.g. whole grains,<sup>20,21,24,25</sup> and specific types of fats (e.g. *trans*<sup>26</sup> and n-3 polyunsaturated fats),<sup>26–31</sup> may be related.<sup>23,32</sup> These nutrient subtypes have not been studied in association with GDM.

In the present paper, we report results from an analysis of diet quality and risk of abnormal glucose tolerance among a cohort of women enrolled in Project Viva, a prospective pregnancy cohort with extensive data on early pregnancy diet. We hypothesised that higher glycaemic load, higher intake of saturated fat, *trans* fat, and red/processed meat, lower intake of n-3 polyunsaturated fat, fibre and whole grain, and following a Western dietary pattern would be independently associated with higher risk of GDM and IGT.

## Methods

### Population and study design

Study subjects were participants in Project Viva, a prospective cohort study of pregnant women and their children. We have previously described recruitment and retention procedures.<sup>33,34</sup> Briefly, we recruited participants at their initial clinical obstetric visit to one of eight clinical sites of a multi-specialty group practice in eastern Massachusetts. Women were eligible to participate if they presented for their initial clinical visit before 22 weeks of gestation, had a

singleton pregnancy, were able to complete study forms in English, and did not plan to move out of the study area prior to delivery. After obtaining informed consent, we collected demographic and health history information by interview and self-administered questionnaire. Institutional review boards of participating institutions approved the study. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki.<sup>35</sup>

Of 2128 participants who delivered a live infant, we excluded those with missing or incomplete records on glucose tolerance testing ( $n = 24$ ), with a history of previous type 1 or type 2 DM or polycystic ovary syndrome with glucose intolerance ( $n = 18$ ), missing ( $n = 332$ ) or implausible (total daily kcal  $<600$  or  $>6000$ ,  $n = 10$ ) information on first trimester diet, or completion of the dietary questionnaire after 26 weeks gestation (i.e. after glucose tolerance screening,  $n = 8$ ) or on an unknown date ( $n = 3$ ). We included the remaining 1733 women in the present analysis. These women did not appreciably differ from the 395 excluded subjects with respect to mean age, height, parity, smoking habits, or incidence of IGT or GDM in the index pregnancy. However, included subjects tended to have a lower pre-pregnancy BMI (24.6 kg/m<sup>2</sup> in included subjects vs. 26.3 kg/m<sup>2</sup> in excluded subjects) and were less likely to be of black (12% vs. 37%) or Hispanic (6.5% vs. 11%) ethnicity, have a low educational attainment (9.4% vs. 25.3% with high school diploma or less), or be in a low income bracket (11.5% vs. 23.8% with household income  $< \$40\,000$ ).

### Dietary assessment

Participants completed self-administered semi-quantitative food frequency questionnaires (FFQ) at two scheduled study visits, one at the initial prenatal visit and the other at 26–28 weeks gestation. For the present analyses, we use data only from the first FFQ, which participants completed at a mean of 11.8 weeks of gestation (range 5–25.6 weeks). We did not use data from the second FFQ because many participants completed it after glucose screening results were available, which may have influenced their diet or its reporting. We modified the FFQ from a well-validated instrument that has been used in the Nurses' Health Study to study associations of nutrients such as glycaemic load and index, fatty acids, and macronutrients with GDM, DM, and cardiovascular health,<sup>17,26,36</sup> and we biochemically validated it for use in pregnancy.<sup>37</sup> The first FFQ asked about the average frequency of consumption 'during this pregnancy' (i.e. since the last menstrual period) of over 140 specified foods as well as additional questions about beverages and preparation methods, including types of fat or oil used for frying, baking and at the table, and whether the participant used stick, tub, or squeezable margarine.

To calculate nutrient intakes, we multiplied a weight assigned to the frequency of use by the nutrient composition for the portion size specified for each food. To obtain estimates of nutrient contents, we used the Harvard nutrient composition database, which is based primarily on US Department of Agriculture publications<sup>38</sup> and is supplemented by other published sources and personal communications from laboratories and manufacturers. Values for *trans* fat contents of foods were supplemented with analyses performed at the Harvard School of Public Health (Department of Nutrition, Boston) of commonly used margarines, shortenings, and baked products in the local area. We then summed contributions to intake across all foods to obtain estimates of total daily intake of all nutrient predictors for each participant.<sup>38</sup> We calculated glycaemic load according to the method of Wolever *et al.*<sup>39</sup> and report the effect of one standard deviation change in intake (32 units, about equivalent to two soft drinks).

Daily food group intake was calculated as follows: whole grains included whole grain bread, brown rice, wheat germ, bran, oat bran, hot breakfast cereal, whole grain cold cereal and other whole grains; processed meats included bacon, hot dogs, sausage, salami, bologna and other processed meats; red meats included beef, lamb, pork or hamburger. For dietary pattern analysis, we grouped food items by nutrient profile or culinary uses into 40 groups, with some

foods comprising their own group (e.g. eggs, pizza, French fries) because of distinctive nutrient content or usage. This is similar to the grouping method used in prior studies of dietary patterns and GDM.<sup>15</sup> We decided not to use alcoholic beverages as a food group, as intake was low in our cohort and results were similar whether or not this group was included. We expressed all macronutrients and fat subtypes (saturated fat, monounsaturated fat, polyunsaturated fat and *trans* fat) as percentage of daily total energy intake. We adjusted all other nutrients [i.e. glycaemic load, fibre, polyunsaturated : saturated fat (P : S) ratio, n-3 fatty acids, n-6 fatty acids and n-6/n-3 ratio] for total energy using the multivariable residual method, which provides an estimate of nutrient effect independent of energy intake.<sup>40</sup> The residual method creates a nutrient variable that has no correlation with total energy intake, thereby removing extraneous variation in the predictor nutrient and resultant spurious associations of the predictor nutrient and outcome, as may happen when the outcome itself is associated with total energy intake.

### Glucose tolerance outcomes

Participating women were routinely screened by their clinicians for gestational diabetes at 26–28 weeks of gestation with a non-fasting oral glucose challenge test, in which venous blood was sampled 1 h after a 50 g oral glucose load. If the 1 h glucose result was  $\geq 140$  mg/dL, the participant was referred for a fasting glucose tolerance test. In that 3 h test, a 100 g oral glucose load was administered in the morning after an overnight fast; normal results were a blood glucose  $< 95$  mg/dL at baseline,  $< 180$  mg/dL at 1 h,  $< 155$  mg/dL at 2 h and  $< 140$  mg/dL at 3 h.<sup>41</sup> We categorised participants with a normal screening glucose challenge as having normal glucose tolerance; those who failed the challenge test but had 0 or 1 abnormal result on the glucose tolerance test as having IGT, and those who had two or more abnormal glucose tolerance test results as having GDM. For the 39 subjects with incomplete glucose testing data, we reviewed the clinical medical record to assign them to normal glucose tolerance ( $n = 7$ ), IGT ( $n = 10$ ) or GDM ( $n = 22$ ).

### Sociodemographic data

At the first study visit, subjects reported their race/ ethnicity, history of GDM in a prior pregnancy, history of DM of any type in the participant's own mother, height, and pre-pregnancy weight (which we used to calculate BMI). We obtained parity (defined as number of previous viable pregnancies) and serial maternal weights from prenatal outpatient medical records, and calculated weight gain up to 26 weeks gestation (around the time of glucose tolerance screening) by subtracting pre-pregnancy weight from the last measured weight at or before 26 weeks. We assessed smoking habits at both study visits and categorised smoking as ever/never smoked during this pregnancy. Subjects reported early pregnancy television viewing habits and physical activity<sup>42</sup> at the second study visit.

### Statistical analysis

All nutrient and food intake variables except whole grains, red meats and processed meats were approximately normally distributed. To allow a common analytical approach for all variables, and to allow for slight non-normality, we used Kruskal–Wallis tests (with a Bonferroni correction) for continuous exposures and chi-square tests for categorical exposures to investigate hypothesised relationships of dietary variables and participant characteristics with IGT and GDM. We examined Spearman correlations among nutrients.

We used multinomial regression<sup>43</sup> to study the associations of established GDM risk factors and individual nutrient types with development of IGT and GDM. Multinomial regression calculates the odds of having either GDM or IGT compared with the reference group, normal glucose tolerance. Our crude model was adjusted for maternal age. In multivariable analyses, we included in the model a priori risk factors for GDM, which included maternal age, pre-

pregnancy BMI, race/ethnicity (white/black/Hispanic/other), family history of DM, history of GDM in a prior pregnancy, and smoking in the index pregnancy. We used white race as reference in analyses based on prior reports of lower GDM rates in this population.<sup>7</sup> Our variable for history of GDM in a prior pregnancy includes three levels (primiparous, parous with no history of GDM, parous with history of GDM), and thus accounts for parity as well. We added potential confounders (e.g. weight gain to 26 weeks gestation, early pregnancy physical activity, and early pregnancy TV viewing habits) to the model one at a time to test whether they resulted in a >10% change in the effect size of nutrient estimates, but none did. As total energy was not associated with IGT or GDM, and did not appreciably change effect estimates for individual nutrients, we did not include it in our analyses.

To examine the effect of carbohydrates, glycaemic load, fibre, and whole grain intake independent of their inverse relationship with fat intake, we added total fat intake to the model in a separate step. We also included total fat intake as a separate step in analyses of fat subtypes (i.e. saturated, monounsaturated, polyunsaturated and *trans* fats), thereby controlling for the effect of all other fat constituents other than the fat subtype of interest. We additionally performed stratified analyses according to pre-pregnancy BMI (< or  $\geq 25$  kg/m<sup>2</sup>).

We then created energy partition models and nutrient density substitution models to study the simultaneous effects of different macronutrients on IGT and GDM risk. Energy partition models examine the effect of adding a specific macronutrient to the diet, while holding the other macronutrients constant. In these models we included calories from total fat, protein and carbohydrates, but not total energy. The coefficient for a specific macronutrient in this model can be interpreted as adding 100 kcal of that macronutrient to the diet, while holding the absolute intake of other macro-nutrients steady. Nutrient density substitution models evaluate the effect of substituting macronutrients for each other in an isocaloric diet; we created models including nutrient densities of total fat, carbohydrates and protein, as well as total energy intake. In this analysis the coefficient for fat, for example, in a model also containing protein and total energy can be interpreted as the effect of exchanging calories from carbohydrate with the same number of calories from fat. These models are similar to those used by Saldana *et al.*<sup>14</sup>

Using nutrient density substitution models, we also examined the effect of replacing one fat subtype for another by including nutrient density variables for all but one fat subtype in a multivariable model along with total fat intake and total energy intake.<sup>40</sup> For example, the coefficient for saturated fat nutrient density in a model also containing monounsaturated fat, *trans* fat, total fat and total energy – but not polyunsaturated fat – can be interpreted as the effect of replacing 1% of calories from polyunsaturated fat with calories from saturated fat.

For dietary pattern analysis, we used principal component factor analysis to identify patterns of correlated food groups, and used an orthogonal rotation procedure to ensure factors themselves were uncorrelated. We retained factors based on eigenvalue, the Scree test and interpretability. We assigned each participant a factor score for each dietary pattern, calculated by summing intakes of food groups multiplied by their factor loadings (i.e. the correlation between a food group and the dietary pattern). A factor score, therefore, represents how closely a participant's diet resembles each common dietary pattern identified within the cohort. We then used multinomial logistic regression to calculate odds ratios by quartile of dietary pattern score, using the lowest quartile as reference. To calculate *P* for trend, we assigned the median value to subjects in each quartile and modelled the variable as a continuous predictor. To facilitate comparison with prior studies, we repeated analyses calculating dietary pattern scores using key food items previously identified<sup>15</sup> (prudent pattern comprising fruits, tomatoes, cabbages, green leafy vegetables, dark yellow vegetables, legumes, other vegetables, poultry and fish; Western pattern comprising red meat, processed meat, refined grains, snacks, sweets, and desserts, French fries and pizza) without weighting by factor loadings.



Because women with prior GDM are at higher risk of GDM in a subsequent pregnancy and may modify their early pregnancy diet accordingly, we repeated all analyses after excluding women who reported a history of GDM ( $n = 31$ ). We performed all analyses using sas version 8.2 (Cary, NC, USA).

## Results

Among the 1733 participants, mean (standard deviation) age was 32.2 (4.9) years, pre-pregnancy BMI was 24.6 (5.3) kg/m<sup>2</sup> and 28% classified themselves as other than white. Mean (standard deviation) daily energy intake assessed by FFQ was 2060 (674) kcal; on average, fat made up 28.2% and carbohydrates made up 55.5% of total calories. Overall, 206 (12%) developed IGT and 91 (5%) women developed GDM. In bivariate analyses, women with IGT and GDM were older, had higher pre-pregnancy BMI, were more likely to have had GDM in a previous pregnancy, and to report that their mothers had a history of DM (data not shown). Women who developed IGT reported less total physical activity during early pregnancy, while women with GDM tended to gain less weight prior to 26 weeks of gestation (data not shown), but neither was independently associated with IGT or GDM in multivariable models. We observed no differences in IGT or GDM rates by maternal height, education, household income, television viewing habits or smoking habits (data not shown).

Table 1 shows multivariable-adjusted associations of participant characteristics with risk of IGT and GDM. After adjustment for all other risk factors, having a BMI above 30 kg/m<sup>2</sup> (vs. <25 kg/m<sup>2</sup>) was associated with elevated odds for both IGT (OR 1.65 [95% CI 1.08, 2.53]) and GDM (OR 3.44 [95% CI 1.88, 6.31]). History of GDM in a prior pregnancy also increased risk of IGT (OR 4.33 [95% CI 1.17, 16.0]) and GDM (OR 58.3 [95% CI 21.1, 161]). Family history of DM was associated with increased risk of IGT only and Hispanic ethnicity with GDM only.

Energy-adjusted nutrient intercorrelations are shown in Table 2. Intake of fat was inversely correlated with that of carbohydrates ( $r = -0.87$ ) and glycaemic load ( $r = -0.72$ ). Intakes of specific types of fat tended to correlate with one another: for example, intake of saturated fat was correlated with intakes of monounsaturated ( $r = 0.71$ ), *trans* ( $r = 0.56$ ) and polyunsaturated fat ( $r = 0.28$ ).

Results of bivariate analyses of dietary variables and glucose tolerance are shown in Table 3, along with nutrient distributions according to glucose tolerance status. Women with IGT had lower average dietary glycaemic load and slightly higher intake of total energy, total fat, saturated fat, fibre and whole grains than normoglycaemic women. Women with GDM had higher average n-3 fatty acid intake, lower n-6/n-3 ratio, and slightly higher polyunsaturated fat intake than normoglycaemic women (Table 3). The only nutrient to show a statistically significant relationship with glucose tolerance was n-3 fatty acids ( $P = 0.02$ ), but after Bonferroni correction for all 30 comparisons in the table, the  $P$ -value was no longer small enough to reject the null hypothesis.

After adjustment for maternal age, pre-pregnancy BMI, race/ethnicity, history of GDM, family history of DM, and smoking during pregnancy, intakes of most nutrients were not associated with risk of developing GDM or IGT (Table 4). Age-adjusted estimates for nutrient intakes were almost identical to multivariable-adjusted estimates and therefore are not shown. In particular, macronutrients linked to GDM in prior studies, including total fat (adjusted OR 1.00 [95% CI 0.96, 1.05] per 1% of energy), carbohydrates (OR 0.99 [95% CI 0.92, 1.06] per 1% of energy), saturated fat (OR 0.98 [95% CI 0.88, 1.08] per 1% of energy), and polyunsaturated fat (OR 1.09 [95% CI 0.94, 1.26] per 1% of energy), were not associated with GDM in this cohort. Additional adjustment of each fat type for total fat intake in a separate step did not

materially change results (data not shown). Total fibre intake was not associated with glucose tolerance, so we examined the soluble and insoluble fibre as separate predictors, with similar results (data not shown). In additional analyses, we broke all nutrient variables into quartiles, and used indicator variables for the quartiles as predictors. We observed no threshold effect or evidence of a nonlinear relationship for any nutrient (data not shown).

The only nutrient with an apparent association with GDM was total n-3 fatty acids: for each 300 mg/day intake, the OR [95% CI] was 1.11 [1.02, 1.22]. A 1-unit increase in the n-6/n-3 ratio was associated with an odds ratio [95% CI] for GDM of 0.93 [0.84, 1.02]. Adjusting for total fat intake did not change these estimates materially. To further explore the direct association of n-3 fatty acids with GDM risk, we conducted *post hoc* analyses examining the association of the individual n-3 fatty acids [docosahexaenoic acid (DHA; 22:6n-3), eicosapentaenoic acid (EPA; 20:5n-3), docosapentaenoic acid (DPA; 22:5n-3), and alpha-linolenic acid (ALA; 18:3n-3)] and their primary food sources with GDM risk. Only ALA was associated with increased risk for GDM, with an OR [95% CI] of 1.29 [1.04, 1.60] per each 300 mg/day after adjustment for confounders and other fats. However, none of the primary food contributors to ALA intake (mayonnaise, oil-based salad dressing, dark bread, chicken, margarine, pizza and muffins) was associated with increased GDM risk after adjustment for confounders (data not shown).

We identified 1119 women with pre-pregnancy BMI < 25 kg/m<sup>2</sup>, and 610 women with BMI ≥ 25 kg/m<sup>2</sup> (four women had missing BMI data). The increased GDM risk associated with n-3 fatty acid intake was limited to the group with BMI < 25 kg/m<sup>2</sup> (adjusted OR: 1.19 [95% CI 1.06, 1.35] per 300 g/day vs. 1.03 [0.83, 1.27] in subjects with BMI ≥ 25 kg/m<sup>2</sup>). Higher intake of total polyunsaturated fats (1.38 [1.08, 1.77] per each 1% increase in calories) and n-6 fatty acids (1.16 [1.02, 1.32] per each 1 g/day) also appeared to increase GDM risk in subjects with pre-pregnancy BMI < 25 kg/m<sup>2</sup>.

Unlike previous findings reported by Saldana *et al.*,<sup>14</sup> we saw no evidence that adding fat or carbohydrates to the diet, or substituting fat for carbohydrates, fat for protein, or carbohydrates for protein was associated with altered risk for GDM or IGT. Substituting one type of fat for another had no effect on risk for IGT or GDM (Table 5).

We identified two dominant dietary patterns within the Project Viva cohort: the prudent pattern, high in vegetables, fruit, legumes, fish, poultry, eggs, salad dressing and whole grains; and the Western pattern, which included red and processed meats, sugar-sweetened beverages, French fries, high-fat dairy products, desserts, butter and refined grains. These patterns explained 11.8% and 6.9% of the variability in dietary intake in our cohort respectively. Neither dietary pattern was associated with risk of IGT or GDM, when examined as continuous variables or in quartiles: adjusted ORs [95% CIs] for GDM across increasing quartiles of Western pattern scores were 1.00 (reference), 1.14 [0.56, 2.29], 1.63 [0.84, 3.19], 0.87 [0.41, 1.83] (*P* for trend = 0.80); and for prudent pattern scores were 1.00 (reference), 0.56 [0.26, 1.21], 1.06 [0.55, 2.05], 1.13 [0.59, 2.16] (*P* for trend = 0.35). Due to concerns that insufficient power was causing wide confidence intervals, we repeated analyses with a combined IGT/GDM outcome, with similar findings. Secondary analyses using simplified pattern scores yielded similar results (data not shown).

For all analyses, excluding subjects with a history of GDM in a previous pregnancy did not materially change the results (data not shown).

## Discussion

In this prospective study, with the possible exception of a detrimental effect of n-3 fatty acid intake in normal-weight women, we saw no evidence that diet quality in early pregnancy,

namely, intake of macronutrients, fat subtypes, whole grains, fibre, glycaemic load, red or processed meats, or dietary patterns, was associated with risk of developing impaired glucose tolerance or gestational diabetes mellitus. We confirmed that previously established risk factors for GDM, including pre-pregnancy BMI, age, race/ethnicity, history of GDM and family history of DM, are strong independent predictors of glucose tolerance.

Our data do not support an influence of total carbohydrate intake or of carbohydrate quality including whole grains, fibre, and dietary glycaemic load on the risk of IGT or GDM. The confidence intervals for carbohydrate intake in the present study are narrow enough to exclude the previously reported effect on GDM risk (OR: 0.90 [95% CI 0.85, 0.98]<sup>14</sup> for adding 100 kcal of carbohydrates to the diet). Although, in our study, confidence intervals for fibre and glycaemic load were wide, they do exclude effect sizes seen in studies of pre-pregnancy diet and GDM in larger cohorts, e.g. relative risks of 0.67 and 1.61 comparing highest with lowest quintile of fibre and glycaemic load respectively.<sup>16</sup> Our results are consistent with two case-control studies that also did not find fibre<sup>11,13</sup> or complex carbohydrates<sup>11</sup> to be related to GDM.

The use of glycaemic index and load in epidemiological studies has limitations. Although glycaemic index can be measured by the rise in blood glucose after ingestion of a food in a laboratory setting, foods take on different glycaemic profiles in the context of mixed meals and with different preparation methods.<sup>23</sup> The nutrient composition database for glycaemic index is not as well developed as for other nutrients, in part for this reason, and it is not clear whether FFQs are able to accurately assess glycaemic index.<sup>44</sup> Because glycaemic load represents both quality and quantity of carbohydrate intake, it may be more appropriate to examine glycaemic load in a multivariable model with total energy intake, fat, and protein, in which the glycaemic load coefficient reflects the effect of replacing low glycaemic index carbohydrates with high glycaemic index carbohydrates;<sup>16</sup> we performed this analysis, with largely similar results (data not shown).

As with carbohydrates, the confidence intervals for fats were fairly narrow, which excludes the effects of total fat, saturated fat and polyunsaturated fat on IGT or GDM observed in other studies.<sup>11,14</sup> Our results excluded a substantial harmful effect of *trans* fats, which trended towards a protective effect against IGT and GDM in substitution models, although with broad confidence intervals. After stratification by pre-pregnancy BMI, increasing polyunsaturated fat intake was associated with elevated GDM risk in subjects with BMI below 25 kg/m<sup>2</sup>, which is unexpected given some evidence to the contrary with regard to DM in non-pregnant adults.<sup>26,30,31</sup> This finding may in part result from intake of the parent n-3 fatty acid ALA, which is a component of and highly correlated with total polyunsaturated fat intake (spearman  $r = 0.83$ ), and is positively associated with GDM in this cohort. To our knowledge, no published data show a detrimental effect of ALA on glucose tolerance. In fact, some animal and human data have suggested that ALA intake is related to improved insulin sensitivity.<sup>45-47</sup> Several reports have noted worsening glycaemic control in diabetics taking elongated n-3 fatty acid supplements,<sup>48-51</sup> but these long-chain fats were not related to GDM risk in this cohort. Given the several predictors examined in our analysis, the positive association of ALA with GDM risk probably results from chance, especially as it was limited to a subset of women.

We also examined the effects of certain food groups and dietary patterns on glucose tolerance. Contrary to recent evidence,<sup>15</sup> red and processed meat intake did not predict GDM risk in our cohort, nor did the type of dietary pattern to which subjects adhered. The use of data-driven dietary patterns has received criticism because of its arbitrary and population-specific nature,<sup>52-54</sup> but the components of our Western and prudent patterns were similar to those of several prior publications,<sup>15,55,56</sup> and results remained null when we used simplified, unweighted patterns.



Only six previous studies have examined associations of diet with GDM. Two were case-control,<sup>11,12</sup> and recall bias may have influenced their findings that GDM was associated with a diet high in total fat<sup>12</sup> and saturated fat<sup>11</sup> and low in polyunsaturated fat.<sup>11</sup> Another study that supported a protective effect of polyunsaturated fat was conducted among Chinese women with little variation in dietary habits or fat sources, which limits the generalisability of their results to western populations.<sup>13</sup> In a well-designed prospective cohort study, Saldana *et al.*<sup>14</sup> found that higher total fat intake increased risk for IGT and GDM when accompanied by a decrease in carbohydrate intake, while carbohydrates were protective when fat intake reciprocally decreased. However, these investigators did not examine the effect of types of fat or quality of carbohydrate, which are more important predictors of glucose intolerance in pregnant<sup>16</sup> and non-pregnant populations.<sup>23,32</sup> They also assessed diet in the second trimester, while we used data obtained in the first trimester of pregnancy because our medical record review suggested that, by later in pregnancy, many subjects had already changed their diet based on heightened risk of GDM and subsequent counselling by healthcare providers. High carbohydrate intake may have appeared protective in the Saldana *et al.* study, if high-risk women were advised to cut down on carbohydrate intake, before exposure ascertainment was complete or GDM was formally diagnosed.

The dissimilarities between our results and those of two large Nurses' Health Study II publications<sup>15,16</sup> do not necessarily imply incompatibility. In over 13 000 women, Zhang *et al.* assessed diet in 1991 and 1995 with a FFQ similar to ours, except that it asked about diet 'over the past year'; 758 self-reported GDM cases developed by 1998. As diet was measured as many as 4 years prior to GDM incidence, theirs is really a study of diet on long-term GDM risk, while we specifically assessed diet since conception. It may be the case that, once insulin resistance has been established from years of dietary patterns characterised by high glycaemic load, low fibre, and high red and processed meat intake, and augmented by the metabolic demands of pregnancy, what women eat in the first few months of pregnancy has relatively little additional effect on risk. This hypothesis is compatible with our findings that physical activity habits before pregnancy have a greater influence on GDM risk than such habits in early pregnancy.<sup>9</sup> Considerable statistical power and multiple dietary assessments, which serve to reduce random error in dietary data, are also likely to have sharpened their ability to observe an effect. These studies are principally limited by residual confounding by pre-pregnancy BMI due to less precise BMI assessment, as BMI was self-reported only at study enrolment.

### Strengths and limitations

Our study had several strengths, including prospective design, relatively large sample size and dietary assessment with a validated FFQ. Few studies of diet and GDM have controlled for nutrient confounding, which is necessary due to high positive and negative intercorrelations between many nutrients. In particular, our null findings were not the result of negative confounding by fat intake. False null associations can also occur when there is insufficient variability in the predictor of interest. Our nutrient intake distributions, however, were similar to those in other studies of diet and GDM.<sup>11,12,14</sup> Project Viva has a relatively high proportion of white, well-educated women from higher income strata, so results may not be generalisable to more disadvantaged populations.

Other limitations characteristic of any nutritional epidemiological study are worthy of mention. Misclassification of exposure with food frequency questionnaire data is inevitable. The Harvard nutrient database calculates nutrient values by averaging the chemically quantified nutrient contents of a sampling of food brands, recipes and geographic regions, providing averaged nutrient values for commonly eaten foods in the United States. Therefore, values will tend to have more error when sample-to-sample variability is high, for micronutrients found in only few foods or, as in the case with *trans* fats, when content in many foods has not been

well characterised. Such sources of error would tend to misclassify participants with respect to exposure and would bias results towards the null. However, calculated intakes for energy and macronutrients from nutrient databases fall within 5–10% of chemically analysed values for the same foods.<sup>40</sup>

Another source of bias is differential reporting by participant subgroups. Women with higher BMI tend to under-report intake of all foods and nutrients.<sup>57-60</sup> When under-reporting of nutrients is in direct proportion to that of total energy intake, energy-adjusting and inclusion of BMI in multivariable models should minimise the bias in nutrient–disease relationships. However, it is possible that subjects with higher BMI may preferentially under-report certain foods or nutrients (e.g. junk foods), which introduces a source of confounding that is difficult to account for statistically. Finally, residual confounding by other ‘healthy lifestyle’ factors may account for positive findings in nutritional epidemiology studies, but this is not likely to be a source of confounding in our largely null study.

We conclude that nutritional status on entering pregnancy, as reflected in pre-pregnancy BMI, is a stronger predictor of abnormal glucose tolerance than any dietary influences during early pregnancy. Whereas diet quality may influence DM and GDM incidence over the long term, the relatively short duration of a single pregnancy may not allow time for diet to affect the risk for GDM. Our results suggest that efforts to reduce rates of GDM should continue to focus on reducing obesity prevalence among women of child-bearing age.

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**Table 1**

Prevalence of established risk factors for gestational diabetes mellitus among 1733 women in Project Viva, and their associations with impaired glucose tolerance and gestational diabetes. All estimates are simultaneously adjusted for all other characteristics in the table

	Entire cohort (N = 1733) n (%)	Impaired glucose tolerance (n = 206) OR [95% CI]	Gestational diabetes mellitus (n = 91) OR [95% CI]
Pre-pregnancy BMI (kg/m <sup>2</sup> )			
<25	1119 (65%)	1.00 Reference	1.00 Reference
25-<30	371 (21%)	1.18 [0.81, 1.72]	1.70 [0.94, 3.06]
≥30	239 (14%)	1.65 [1.08, 2.53]	3.44 [1.88, 6.31]
Age category (years)			
14–24	125 (7%)	1.00 Reference	1.00 Reference
25–34	1111 (64%)	2.03 [0.85, 4.85]	4.84 [0.98, 23.8]
35–39	421 (24%)	2.49 [1.01, 6.16]	2.96 [0.55, 15.9]
40+	76 (4%)	4.22 [1.49, 11.9]	11.3 [1.86, 68.5]
Race/ethnicity			
White	1252 (72%)	1.00 Reference	1.00 Reference
Black	210 (12%)	0.68 [0.41, 1.16]	0.66 [0.29, 1.52]
Hispanic	112 (6%)	1.35 [0.73, 2.47]	3.19 [1.51, 6.71]
Other	159 (9%)	0.40 [0.19, 0.84]	1.31 [0.61, 2.84]
Gestational diabetes in a prior pregnancy			
No	1150 (67%)	1.00 Reference	1.00 Reference
Yes	31 (2%)	4.33 [1.17, 16.0]	58.3 [21.1, 161]
Primiparous	543 (32%)	0.84 [0.59, 1.19]	1.12 [0.65, 1.94]
DM in participant's mother			
No	1536 (89%)	1.00 Reference	1.00 Reference
Yes	121 (7%)	2.44 [1.50, 3.97]	1.48 [0.66, 3.32]
Missing/don't know	76 (4%)	0.68 [0.26, 1.73]	0.93 [0.27, 3.18]
Smoking during this pregnancy	46 (3%)	1.60 [0.71, 3.60]	1.17 [0.27, 5.13]

BMI, body mass index; DM, diabetes mellitus.

**Table 2** Spearman correlations among nutrients measured by food frequency questionnaire in the first trimester of pregnancy among 1733 women in Project Viva

	Glycaemic load <sup>a</sup>	Carbohydrates <sup>b</sup>	Total fat <sup>b</sup>	Trans fat <sup>b</sup>	Saturated fat <sup>b</sup>	Polyunsaturated fat <sup>b</sup>	Monounsaturated fat <sup>b</sup>	n-3 Fatty acids <sup>a</sup>	n-6 Fatty acids <sup>a</sup>	Red meat	Processed meat
Glycaemic load <sup>a</sup>	1										
Carbohydrates <sup>a</sup>	0.86	1									
Total fat <sup>b</sup>	-0.72	-0.87	1								
Trans fat <sup>b</sup>	-0.27	-0.44	0.60	1							
Saturated fat <sup>b</sup>	-0.64	-0.73	0.83	0.56	1						
Polyunsaturated fat <sup>b</sup>	-0.42	-0.56	0.66	0.31	0.28	1					
Monounsaturated fat <sup>b</sup>	-0.69	-0.84	0.93	0.56	0.71	0.53	1				
n-3 Fatty acids <sup>a</sup>	-0.41	-0.51	0.54	0.25	0.27	0.79	0.41	1			
n-6 Fatty acids <sup>a</sup>	-0.40	-0.54	0.64	0.31	0.26	0.99	0.52	0.74	1		
Red meat	-0.33	-0.44	0.41	0.37	0.35	0.12	0.47	0.09	0.08	1	
Processed meat	-0.16	-0.28	0.37	0.33	0.32	0.20	0.38	0.17	0.18	0.35	1
Fibre <sup>a</sup>	0.16	0.40	-0.42	-0.47	-0.47	-0.19	-0.37	-0.24	-0.20	-0.25	-0.32
Whole grains	0.07	0.12	-0.16	-0.25	-0.19	-0.008	-0.15	-0.08	-0.03	-0.03	-0.17

<sup>a</sup>  $P < 0.0001$  where  $|r| \geq 0.09$ ;  $P < 0.01$  where  $0.07 \geq |r| \geq 0.08$ ;  $P < 0.05$  where  $0.05 \geq |r| > 0.07$ .

<sup>b</sup> Energy-adjusted by the 5% residual method.

<sup>c</sup> Nutrient density.

Table 3

Daily intakes of energy, nutrients, and foods in the first trimester of pregnancy among women with normal glucose tolerance, impaired glucose tolerance or gestational diabetes mellitus: data from 1733 pregnant women in Project Viva

1st trimester diet	Normal glucose tolerance ( <i>n</i> = 1436) Mean (SD): 25th, [50th, 75th %ile]	Impaired glucose tolerance ( <i>n</i> = 206) Mean (SD): 25th, [50th, 75th %ile]	Gestational diabetes mellitus ( <i>n</i> = 91) Mean (SD): 25th, [50th, 75th %ile]
Total energy (kcal)	2049 (674): [1593, 1984, 2398]	2117 (675): [1673, 2088, 2437]	2090 (666): [1619, 1971, 2411]
Glycaemic load <sup>d</sup>	211.0 (32): [190.9, 210.1, 229.8]	206.4 (30): [185.9, 204.5, 224.8]	207.6 (36): [188.9, 210.0, 226.5]
Carbohydrates (% energy)	55.6 (7.1): [51.1, 55.3, 60.3]	54.9 (6.9): [50.4, 54.8, 59.0]	54.7 (7.9): [50.1, 56.1, 60.8]
Fat (% energy)	28.1 (5.4): [24.5, 28.2, 31.6]	28.8 (5.3): [24.8, 28.8, 32.5]	28.5 (5.8): [24.6, 27.0, 32.5]
<i>Trans</i> fats (% energy)	1.36 (0.46): [1.05, 1.33, 1.62]	1.36 (0.46): [1.00, 1.31, 1.61]	1.37 (0.41): [1.02, 1.38, 1.66]
Saturated fats (% energy)	10.4 (2.5): [8.8, 10.3, 12.1]	10.8 (2.5): [9.2, 10.8, 12.4]	10.4 (2.4): [8.8, 10.0, 11.7]
Poly fats (% energy)	6.1 (1.5): [4.9, 5.9, 7.0]	6.1 (1.6): [5.0, 5.9, 7.1]	6.3 (1.9): [5.1, 6.0, 7.5]
Mono fats (% energy)	10.6 (2.4): [9.0, 10.6, 12.2]	10.8 (2.4): [9.1, 10.7, 12.5]	10.7 (2.6): [8.9, 10.2, 12.2]
P : S ratio <sup>d</sup>	0.61 (0.20): [47.7, 57.1, 69.4]	0.59 (0.20): [0.46, 0.55, 0.69]	0.62 (0.18): [0.51, 0.61, 0.73]
n-3 fatty acids <sup>d</sup> (g)	1.12 (0.47): [0.81, 1.05, 1.33]	1.16 (0.69): [0.81, 1.06, 1.34]	1.29 (0.79): [0.84, 1.17, 1.52]
n-6 fatty acids <sup>d</sup> (g)	11.8 (3.1): [9.6, 11.6, 13.7]	11.9 (3.1): [9.7, 11.4, 14.0]	12.3 (3.6): [9.7, 11.6, 14.6]
n-6/3 ratio <sup>d</sup>	11.3 (3.9): [9.4, 10.8, 12.5]	11.1 (3.1): [9.3, 10.6, 12.5]	10.5 (2.7): [9.0, 10.0, 11.9]
Fibre <sup>d</sup> (g)	19.8 (5.8): [15.9, 19.1, 23.0]	20.5 (6.0): [16.6, 20.2, 23.5]	19.0 (5.1): [15.1, 19.0, 22.2]
Whole grains (servings)	1.22 (1.2): [0.42, 0.93, 1.65]	1.34 (1.2): [0.50, 0.97, 2.00]	1.12 (1.1): [0.21, 0.85, 1.57]
Red meat (servings)	0.38 (0.32): [0.21, 0.28, 0.49]	0.41 (0.37): [0.21, 0.35, 0.49]	0.43 (0.33): [0.21, 0.35, 0.57]
Processed meat (servings)	0.21 (0.27): [0.00, 0.14, 0.28]	0.23 (0.35): [0.07, 0.14, 0.28]	0.22 (0.30): [0.07, 0.14, 0.28]

P : S, Polyunsaturated : saturated fat.

<sup>d</sup>Energy-adjusted by the residual method.

**Table 4**

Adjusted<sup>a</sup> associations of first trimester intake of foods and energy-adjusted nutrients with impaired glucose tolerance and gestational diabetes mellitus among 1733 women in Project Viva

Daily intake	Impaired glucose tolerance OR [95% CI]	Gestational diabetes mellitus OR [95% CI]
Energy (per 100 kcal)	1.01 [0.99, 1.03]	1.00 [0.97, 1.04]
Carbohydrates (% energy)	1.00 [0.98, 1.02]	1.00 [0.96, 1.03]
Glycaemic load (per 1 SD = 32.0 units)	0.95 [0.82, 1.12]	0.96 [0.76, 1.22]
Total fat (% energy)	1.01 [0.98, 1.04]	1.00 [0.96, 1.05]
Saturated fat (% energy)	1.03 [0.97, 1.10]	0.98 [0.88, 1.08]
Polyunsaturated fat (% energy)	1.01 [0.92, 1.11]	1.09 [0.94, 1.26]
Monounsaturated fat (% energy)	1.02 [0.95, 1.08]	1.00 [0.91, 1.11]
<i>Trans</i> fat (% energy)	0.93 [0.66, 1.31]	0.87 [0.51, 1.49]
P : S ratio (per 1%)	1.00 [0.99, 1.01]	1.01 [0.99, 1.02]
n-3 fatty acids (per 300 mg)	1.03 [0.95, 1.12]	1.11 [1.02, 1.22]
n-6 fatty acids (per 1 g)	1.00 [0.95, 1.05]	1.03 [0.96, 1.11]
n-6/n-3 ratio (per unit)	0.99 [0.95, 1.03]	0.93 [0.84, 1.02]
Fibre (per 5 g)	1.07 [0.94, 1.23]	0.92 [0.74, 1.15]
Whole grains (per serving)	1.05 [0.92, 1.19]	0.90 [0.73, 1.13]
Red meat (per weekly serving)	1.01 [0.95, 1.08]	1.01 [0.91, 1.12]
Processed meat (per weekly serving)	1.02 [0.94, 1.10]	0.95 [0.85, 1.06]

P : S, Polyunsaturated : saturated fat.

<sup>a</sup>Other covariates included in the model were: maternal age, pre-pregnancy body mass index, race/ethnicity, previous gestational diabetes, history of diabetes in participant's mother, and smoking during pregnancy.

**Table 5**

Macronutrient energy partition and nutrient density substitution models: adjusted<sup>a</sup> odds ratios [95% CI] for risk for abnormal glucose tolerance among 1733 women in Project Viva

	Impaired glucose tolerance OR [95% CI]	Gestational diabetes mellitus OR [95% CI]
Adding 100 kcal fat to diet	1.07 [0.95, 1.19]	0.99 [0.82, 1.18]
Adding 100 kcal carbohydrates to diet	1.00 [0.95, 1.06]	0.99 [0.91, 1.08]
Substituting 1% of calories from fat for carbohydrates (isocaloric)	1.01 [0.98, 1.04]	1.00 [0.96, 1.05]
Substituting 1% of calories from fat for protein (isocaloric)	1.04 [0.98, 1.10]	0.99 [0.90, 1.09]
Substituting 1% of calories from carbohydrates for protein (isocaloric)	1.02 [0.98, 1.07]	0.99 [0.92, 1.06]
Substituting 1% of calories from polyunsaturated fat with:		
<i>Trans</i> fat	0.77 [0.50, 1.20]	0.81 [0.42, 1.56]
Saturated fat	1.05 [0.93, 1.19]	0.90 [0.75, 1.08]
Monounsaturated fat	0.98 [0.82, 1.18]	0.90 [0.68, 1.21]
Substituting 1% of calories from monounsaturated fat with:		
<i>Trans</i> fat	0.77 [0.50, 1.20]	0.84 [0.44, 1.62]
Saturated fat	1.06 [0.91, 1.23]	0.99 [0.77, 1.26]
Polyunsaturated fat	1.00 [0.84, 1.20]	1.13 [0.85, 1.50]
Substituting 1% of calories from saturated fat with:		
<i>Trans</i> fat	0.76 [0.49, 1.19]	0.84 [0.44, 1.63]
Monounsaturated fat	0.93 [0.78, 1.11]	1.02 [0.76, 1.37]
Polyunsaturated fat	0.94 [0.82, 1.08]	1.15 [0.93, 1.43]
Substituting 1% of calories from <i>trans</i> fat with:		
Saturated fat	1.04 [0.77, 1.41]	1.05 [0.58, 1.93]
Monounsaturated fat	0.99 [0.68, 1.42]	1.09 [0.53, 2.25]
Polyunsaturated fat	1.00 [0.71, 1.42]	1.23 [0.61, 2.46]

<sup>a</sup>Other covariates included in the model were: maternal age, pre-pregnancy body mass index, race/ethnicity, previous gestational diabetes, history of diabetes in participant's mother, and smoking during pregnancy.