Longitudinal associations of nutritional factors with glycated hemoglobin in youth with type 1 diabetes: the SEARCH Nutrition Ancillary Study[1–3]

Archana P Lamichhane, Jamie L Crandell, Lindsay M Jaacks, Sarah C Couch, Jean M Lawrence, and Elizabeth J Mayer-Davis

ABSTRACT

Background: Improved glycated hemoglobin (Hb A_{1c}) delays the progression of microvascular and macrovascular complications in individuals with type 1 diabetes (T1D). We previously showed that higher baseline intakes of n–3 (ω-3) fatty acids and leucine are associated with preserved β cell function 2 y later in youth with T1D.

Objective: In the current study, we extend this work to explore the longitudinal associations of nutritional factors with Hb A_{1c} in youth with T1D.

Design: We included 908 T1D youth with baseline and follow-up Hb A_{1c} measurements. Nutritional factors assessed at baseline were as follows: breastfeeding status and timing of complimentary food introduction; intakes of leucine, carbohydrates, protein, fat, and fiber estimated from a food-frequency questionnaire (FFQ); and plasma biomarkers for vitamins D and E, eicosapentaenoic acid (EPA), and docosahexaenoic acid. We fit linear regression models adjusted for baseline Hb A_{1c}, sociodemographic variables, diabetes-related variables, time between baseline and follow-up visits, saturated fat, physical activity, and for FFQ-derived nutrients, total calories. The vitamin D model was further adjusted for season and body mass index *z* score.

Results: The mean ± SD age and diabetes duration at baseline was 10.8 ± 3.9 y and 10.1 ± 5.8 mo, respectively. A total of 9.3% of participants had poor Hb A_{1c} (value ≥9.5%) at baseline, which increased to 18.3% during follow-up ($P < 0.0001$). Intakes of EPA ($\beta = -0.045$, $P = 0.046$), leucine ($\beta = -0.031$, $P = 0.0004$), and protein ($\beta = -0.003$, $P = 0.0002$) were significantly negatively associated with follow-up Hb A_{1c} after adjustment for confounders. Intake of carbohydrates was significantly positively ($\beta = 0.001$, $P = 0.003$) associated with follow-up Hb A_{1c} after adjustment for confounders.

Conclusions: Several nutritional factors may be associated with Hb A_{1c} during early stages of disease progression in youth recently diagnosed with T1D. In addition to the overall role of major macronutrients such as carbohydrates and protein, leucine and n–3 fatty acid intakes, such as of EPA, may be important for long-term glycemic control. *Am J Clin Nutr* 2015;101:1278–85.

Keywords: Hb A_{1c}, infant feeding practices, macronutrients, nutrient biomarkers, type 1 diabetes

INTRODUCTION

Improved long-term glycemic control, measured by glycated hemoglobin (Hb A_{1c}),[4] was definitively shown to delay the progression of microvascular (1) and macrovascular (2) complications in individuals with type 1 diabetes (T1D). In addition, the preservation of β cell function, measured by the fasting C-peptide (FCP) concentration (3), has been associated with lower Hb A_{1c} and less-frequent microvascular complications (4). Hence, interventions that target an improvement in Hb A_{1c} and sustained β cell function may delay the development of diabetes-related complications. This effect is particularly important because of data from the SEARCH for Diabetes in Youth study that showed ∼17% of youth with T1D in the United States have poor Hb A_{1c} (value ≥9.5%) (5).

Nutritional factors during early life (breastfeeding and timing of the introduction of complimentary foods) (6–8) and childhood (vitamins C, D, and E and long-chain n–3 fatty acids) (7, 9, 10) have been associated with the development of β cell autoimmunity, incident T1D, β cell function, and glycemic control. In addition, we recently showed that long-chain n–3 fatty acid and leucine intakes were significantly positively associated with FCP concentrations ∼2 y postdiagnosis in youth with T1D (11).

[1] From the Department of Nutrition, Gillings School of Global Public Health (APL), the Department of Nutrition, Gillings School of Global Public Health and School of Medicine (EJM-D), and the Departments of Nursing and Biostatistics (JLC), University of North Carolina, Chapel Hill, NC; the Department of Nutritional Sciences, University of Cincinnati Medical Center, Cincinnati, OH (SCC); the Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA (JML), and the Hubert Department of Global Health, Emory University, Atlanta, GA (LMJ).

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[3] Address correspondence to AP Lamichhane, Department of Nutrition, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 2217B McGavran-Greenberg Hall, Campus Box 7461, Chapel Hill, NC 27599. E-mail: archana_lamichhane@unc.edu.

[4] Abbreviations used: FCP, fasting C-peptide; FFQ, food-frequency questionnaire; Hb A_{1c}, glycated hemoglobin; SNAS, SEARCH Nutrition Ancillary Study; T1D, type 1 diabetes.

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The majority of these findings for the associations of nutritional factors with Hb A_{1c} came from studies done in highly controlled settings. Less is known about the impact of micronutrients and macronutrients on Hb A_{1c} in a population-based setting. Particularly, little is known in terms of diet and Hb A_{1c} in the early disease-progression period for T1D. Current dietary guideline for the intensive treatment of T1D emphasize carbohydrate counting for mealtime bolus calculations on the basis of the assumption that carbohydrates are the primary macronutrient that affects postprandial glucose and, thus, insulin requirements (11, 12). However, very little is known about the relation between usual dietary intake and Hb A_{1c} in individuals with T1D.

The aim of the current study was to examine the prospective association of nutritional exposures with Hb A_{1c} in youth with recently diagnosed T1D. On the basis of published findings, including our recent article on the influence of nutritional factors on β cell function (11), we explored associations of the following 3 sets of nutritional exposures with Hb A_{1c}: *1*) infant feeding practices (breastfeeding and introduction of complimentary foods), *2*) baseline plasma biomarkers of selected nutrients (vitamins D and E, EPA, and DHA), and *3*) baseline estimated intake of nutrients from a validated FFQ (of carbohydrate, fat, protein, fiber, and leucine).

METHODS

Study sample

Data for this study were from youth with T1D diagnosed from 2002 through 2005 (incident cases) who participated in the SEARCH for Diabetes in Youth Study (13). Additional data were collected as part of the SEARCH Nutrition Ancillary Study (SNAS). The SEARCH study is a multicenter observational study that began conducting a population-based ascertainment of nongestational cases of diabetes in youth <20 y of age in 2001 and is continuing through the present time. Data were collected during clinic visits at baseline and 12- and 24-mo follow-up visits. Protocols for the SEARCH study and SNAS were reviewed and approved by the local institutional review boards and complied with the Health Insurance Portability and Accountability Act privacy rules. Study participants <18 y old provided informed assent and parental or guardian consent, and participants ≥18 y old provided informed consent at the start of study visits.

We included youth with provider identified type 1, type 1a, or type 1b diabetes (incident: 2002–2005) who had a positive test for at least one diabetes autoantibody (glutamic acid decarboxylase 65 or insulinoma antigen 2) and a baseline Hb A_{1c} measurement and at least one follow-up (12- or 24-mo) Hb A_{1c} measurement (n = 908). We excluded individuals with no follow-up Hb A_{1c} measurements (n = 396) after verifying that this group was sociodemographically similar to those with follow-up data (data not shown). For individuals with 2 follow-up visits, we used the first measured Hb A_{1c} value; most participants (n = 694; 76.4%) had available Hb A_{1c} data from the 12-mo follow-up; 24-mo data were used for the remainder. Sample sizes for the association of nutritional exposures and Hb A_{1c} varied depending on the availability of nutritional exposure data.

Data from the SEARCH study

Fasting blood samples were obtained during in-person clinic visits and under conditions of metabolic stability (i.e., no episode of diabetic ketoacidosis during the previous month). Hb A_{1c} was measured in whole blood by using an automated nonporous ion-exchange HPLC system (model G-7; Tosoh Bioscience) (5). FCP was measured by using a 2-site immunoenzymetric assay (Tosoh AIA; Tosoh Bioscience) (11). Additional details about laboratory methods are shown elsewhere (11).

Data on sociodemographic characteristics and treatment regimens were obtained by interviewing parents (for participants <18 y) or from participants (for participants ≥18 y of age). Weight and height information were used to calculate normalized BMI (in kg/m^2) z scores on the basis of US CDC growth charts (14).

Usual dietary intake for the previous week was assessed by using a validated food-frequency questionnaire (FFQ) for youth ≥10 y old. Details on the dietary assessment methodology and validation in the SEARCH study have been published elsewhere (15). In brief, the SEARCH FFQ consists of 85 food and beverage items queried for weekly frequency. Portion size was estimated as the number of items or in relation to pictures of food in bowls or plates (small, medium, and large). Nutrient and portion-size databases were based on the Nutrition Data Systems for Research (database 3, version 4.05/33 2002; Nutrition Coordinating Center, University of Minnesota). The FFQ was self-administered by participants with support from the study staff as needed. Physical activity was also assessed in youth ≥10 y old in the SEARCH study by using questionnaires from the Youth Risk Behavior Surveillance Systems. Physical activity at baseline was classified as vigorous activity 0–2 or 3–7 d/wk.

Data from the SNAS study

Information on infant diet history was based on maternal self-report and assessed by using a previously validated questionnaire (16). The questionnaire was designed to capture diet information at various intervals of the child's life (first 3 d of life, first week of life, and each month through 12 mo of age). The questionnaire captured detailed information about breastfeeding and formula feeding as well as the introduction of various other food and beverage items such as cow milk, soy milk, fruit and fruit juice, cereals, vegetables, beef, fish, cod liver oil, and vitamins. For this study, we focused on breastfeeding and age at the introduction of complementary foods. Breastfeeding was categorized as never, <6 mo, and ≥6 mo. Age at the introduction of complementary foods was defined as any dairy including formula or any solid food other than breast milk. Age (mo) at the introduction of complimentary foods was noted if the food and beverage items were introduced at least 1 time/wk on a regular basis (11).

Nutritional data on vitamins D and E and the long chain n–3 fatty acids EPA and DHA were assessed in stored serum samples from the baseline SEARCH visit. Details about laboratory methods were published elsewhere (11). Briefly, the concentration of 25-hydroxyvitamin D was measured by using the direct competitive chemiluminescence immunoassay developed by DiaSorin on the basis of a linkage between specific vitamin D

antibody–coated magnetic particles and an isoluminol derivative (detectable range: 5–320 nmol/L). Thirteen samples with 25-hydroxyvitamin D values below the detectable limit were set to 4.9 nmol/L for this analysis. The plasma concentration of α-tocopherol was assayed by using HPLC. For fatty acid measures, total lipids were extracted from plasma by using the Bligh-Dyer method, and phospholipids were separated from all other lipids by using one-dimensional thin-layer chromatography (11). The phospholipid extract was saponified and transmethylated. Gas chromatography was performed on samples dissolved in undecane by using conditions modified from those of Lemaitre et al. (17). Data were analyzed with ChemStation Firmware A.01.09 (Agilent). Plasma phospholipid fatty acids were expressed as the percentage (by weight) of total fatty acids detected.

Statistical analyses

Descriptive analyses were conducted to examine how sociodemographic characteristics and nutritional exposures varied according to baseline Hb A_{1c} categories and to assess threshold effects. Because threshold effects were not evident (data not shown), we performed a linear regression analysis with continuous, log-transformed Hb A_{1c} as the outcome.

We fit a series of models with follow-up Hb A_{1c} as the outcome. We present the results of an unadjusted model (model 1) and a covariate-adjusted model (model 2). Model 1 included baseline Hb A_{1c} and the time between baseline and follow-up Hb A_{1c} measures. Model 2 was further adjusted for potential confounders expected to be associated with β cell function, Hb A_{1c}, and nutritional exposures. These covariates were demographic characteristics (age, sex, race-ethnicity, parental education, and study site), diabetes-related variables (duration, insulin regimen, insulin dose per kilogram of body weight, and fasting glucose), and saturated fat intake (FFQ saturated fat for FFQ-derived nutritional exposures; plasma phospholipid saturated fat otherwise). Exposures from the FFQ were further adjusted for caloric intake and physical activity. Models with vitamin D as the exposure were also adjusted for season of the year in which samples were collected and BMI z score.

As a sensitivity analysis, we also explored associations of non-FFQ nutritional exposures with Hb A_{1c} by further adjusting for physical activity along with the covariates included in model 2. Because physical activity data were available only in youth 10–19 y of age, additional adjustment for physical activity in model 2 for non-FFQ nutritional exposures (which included youth 0–19 y of age) reduced our sample size by almost 40%.

We considered $P < 0.05$ as the level of significance for our analysis. All analyses were conducted with SAS 9.3 software (SAS Institute).

RESULTS

The majority of participants (n = 908) were non-Hispanic whites and had at least one parent with a college degree (**Table 1**). Their mean ± SD age and diabetes duration at baseline were 10.8 ± 3.9 y and 10.1 ± 5.8 mo, respectively. A total of 9.3% of participants had poor Hb A_{1c} (i.e., ≥9.5%) at the baseline visit, and the proportion increased to 18.3% at the follow-up visit (follow-up occurred, on average, 17.9 mo after baseline). Similarly, a decrease in β cell function from baseline to follow-up was observed, whereby the mean ± SD FCP decreased from 0.6 ± 0.6 to 0.4 ± 0.4 μg/L. Changes in both Hb A_{1c} and FCP from baseline to follow-up were significant (both $P < 0.0001$).

The longitudinal associations, which were adjusted for baseline Hb A_{1c} and the time between baseline and follow-up visits, indicated that higher plasma vitamin D at baseline was significantly associated with lower concentrations of follow-up Hb A_{1c} (**Table 2**, model 1). This association was no longer significant after adjustment for potential confounders (Table 2, model 2). Similarly, after adjustment for baseline Hb A_{1c} and the time between visits, higher plasma phospholipid EPA at baseline was significantly associated with lower concentrations of follow-up Hb A_{1c} (Table 2, model 1). This association remained significant after adjustment for additional confounders (Table 2, model 2). Associations of vitamin E and DHA with follow-up Hb A_{1c} were NS in either model. Estimated intake of total carbohydrate at baseline was significantly positively associated with follow-up Hb A_{1c}, and estimated intakes of leucine and total protein at baseline were significantly negatively associated with follow-up Hb A_{1c} in both models (Table 2, models 1 and 2). These associations strengthened after adjustment for potential confounders including saturated fat intake. Models with animal and vegetable proteins also suggested significant negative associations of both protein types with Hb A_{1c}. The strength of the association between vegetable protein and Hb A_{1c} was slightly stronger ($\beta = -0.005$, $P = 0.0003$) than that for animal protein ($\beta = -0.002$, $P = 0.0007$), but the direction of association was the same. Higher estimated intake of total fat tended to be associated with lower Hb A_{1c} at follow-up only in model 1 (Table 2); the association was NS once adjusted for potential confounders in model 2 (Table 2). No significant associations were observed between early life infant feeding exposures or dietary fiber intake and follow-up Hb A_{1c}. Adjustment for FCP in all longitudinal models did not attenuate the association between nutritional exposures and Hb A_{1c} (data not shown).

To put the significant findings into clinical context, we estimated the difference in follow-up Hb A_{1c} predicted by a 1-SD difference in the nutritional exposure at baseline in the fully adjusted model (Table 2, model 2). A 1-SD higher total leucine and 1-SD higher protein intake at baseline were associated with an 8.2% lower Hb A_{1c} percentage and 9.6% lower Hb A_{1c} percentage at follow-up, respectively. Similarly, a 1-SD higher carbohydrate intake at baseline was associated with a 10.0% higher follow-up Hb A_{1c} percentage. These results showed that a predicted Hb A_{1c} of 8% became 7.3%, 7.2%, or 8.8% with a 1-SD increase in leucine, total protein, or total carbohydrate intakes, respectively. The effect of EPA was more modest, with a 1-SD increase in EPA that corresponded to a 1.1% decrease in the follow-up Hb A_{1c} percentage; a predicted Hb A_{1c} of 8% dropped to 7.9% with a 1-SD increase in plasma EPA concentration.

In the sensitivity analysis, additional adjustment for physical activity along with model 2 covariates did not change the direction and significance of associations between non-FFQ exposures and Hb A_{1c} (data not shown).

TABLE 1
Characteristics of youth with type 1 diabetes diagnosed in 2002–2005: the SNAS[1]

Characteristic	*n*	Value
Sociodemographic and clinical characteristics		
Age at visit, y	908	10.8 ± 3.9[2]
Female, %	433	47.7
Race-ethnicity, %		
Non-Hispanic white	707	77.9
African American	82	9.0
Hispanic	102	11.2
Other	17	1.9
Parental education,[3] %		
Less than high school	35	3.9
High school graduate	126	13.9
Some college/associate's degree	316	34.5
Bachelor's degree or more	426	47.2
Duration of diabetes, mo	908	10.1 ± 5.8
Insulin regimen, %		
Pump	81	9.0
Long + short/rapid insulin, ≥3 times/d	303	33.7
Long + any other combination, ≥2 times/d	72	8.0
Any combination of insulin excluding long, ≥3 times/d	130	14.5
Any insulin used 1 time/d or any insulin combination		
Excluding long, twice/d	312	34.7
Insulin dose, units/kg	871	0.6 ± 0.3
Fasting glucose, mmol/L	856	9.6 ± 4.3
Hb A_{1c} value,[4] %		
Baseline Hb A_{1c}	908	7.6 ± 1.4
Follow-up Hb A_{1c}	908	8.6 ± 1.6
Baseline Hb A_{1c} category, %		
<8.5	570	62.8
8.5–9.4	254	28.0
≥9.5	84	9.3
Follow-up Hb A_{1c} category, %		
<8.5	533	58.7
8.5–9.4	209	23.0
≥9.5	166	18.3
FCP,[4] μg/L		
Baseline FCP	854	0.6 ± 0.6
Follow-up FCP	853	0.4 ± 0.4
BMI *z* score	882	0.5 ± 0.9
Physical activity (vigorous activity d/wk),[5] %		
0–2	190	36.7
3–7	515	63.1
Infant feeding exposures		
Breastfeeding, %		
Never	188	27.2
<6 mo	204	29.5
≥6 mo	299	43.3
Age at introduction of complimentary foods, mo		
Any solid food	726	4.6 ± 2.1
Any dairy (including formula)	656	4.8 ± 4.2
Any vegetable (excluding potatoes)	700	6.5 ± 2.1
Gluten-containing cereal	710	6.7 ± 2.7
Baseline nutritional exposures: biomarkers		
Vitamin D [plasma 25(OH)D], nmol/L	807	61.1 ± 34.9
Vitamin E (plasma α-tocopherol), mg/L	704	6.02 ± 3.0
EPA, plasma phospholipid percentage weight	603	0.4 ± 0.2
DHA, plasma phospholipid percentage weight	605	2.4 ± 0.8
Baseline nutritional exposures: estimated from FFQ (g/1000 kcal)[5]		
Leucine	470	3.2 ± 0.5
Total carbohydrate	470	115.5 ± 18.5
Total fat	470	43.3 ± 6.7
Total protein	470	40.0 ± 5.6
Total fiber	470	7.2 ± 2.5

[1]Data are for 908 participants, not all of whom had available data on all variables. FCP, fasting C-peptide; FFQ, food-frequency questionnaire; Hb A_{1c}, glycated hemoglobin; SNAS, SEARCH Nutrition Ancillary Study; 25(OH)D, 25-hydroxyvitamin D.

[2]Mean ± SD (all such values).

[3]Parental education was defined as the highest level of education attained by the father or mother of study participants.

[4]Paired *t* tests indicated that Hb A_{1c} and FCP changes from baseline to follow-up were significant ($P < 0.0001$ for both).

[5]Physical activity and nutritional exposures from the FFQ were available only for youth aged ≥10 y in the SEARCH study.

TABLE 2
Longitudinal associations of nutritional exposures with log Hb A_{1c} for youth with type 1 diabetes (incident: 2002–2005): the SNAS[1]

	Model 1		Model 2	
Nutritional exposures	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*
Infant feeding exposures				
Breastfeeding				
Never	0.020 ± 0.013	0.38	0.004 ± 0.020	0.97
<6 mo	0.007 ± 0.013	—	0.003 ± 0.016	—
≥6 mo	Reference	—	Reference	—
Age at introduction of complimentary foods, mo				
Any solid food	0.0005 ± 0.002	0.84	−0.0009 ± 0.003	0.77
Any dairy (including formula)	−0.002 ± 0.001	0.06	−0.001 ± 0.002	0.51
Any vegetable (excluding potatoes)	0.0004 ± 0.002	0.87	−0.002 ± 0.003	0.58
Gluten-containing cereal	0.001 ± 0.002	0.59	0.003 ± 0.002	0.25
Baseline nutritional exposures: biomarkers				
Vitamin D [plasma 25(OH)D], nmol/L	−0.0006 ± 0.0001	<0.0001	−0.00004 ± 0.0002	0.82
Vitamin E (plasma α-tocopherol), mg/L	−0.002 ± 0.002	0.27	−0.0009 ± 0.002	0.64
EPA (plasma phospholipid percentage weight)	−0.060 ± 0.023	0.01	−0.045 ± 0.023	0.046
DHA (plasma phospholipid percentage weight)	0.001 ± 0.007	0.85	−0.004 ± 0.007	0.59
Baseline nutritional exposures: estimated from FFQ, g				
Leucine	−0.021 ± 0.008	0.01	−0.030 ± 0.009	0.0005
Total carbohydrate	0.0006 ± 0.0002	0.01	0.001 ± 0.0003	0.002
Total fat	−0.001 ± 0.001	0.07	−0.001 ± 0.001	0.17
Total protein	−0.002 ± 0.001	0.003	−0.003 ± 0.001	0.0002
Total fiber	−0.0003 ± 0.002	0.84	−0.0004 ± 0.002	0.85

[1]Analysis consisted of multiple regression models for log Hb A_{1c} at follow-up. Model 1 was adjusted for baseline Hb A_{1c} value and the duration between baseline and follow-up Hb A_{1c} assessments because of the longitudinal design. Model 2 represents the fully adjusted model and included adjustment for demographic characteristics (age at follow-up, sex, race-ethnicity, parental education, and study site), diabetes-related variables at follow-up (duration, insulin regimen, insulin dose, and fasting glucose), and saturated fat at baseline (plasma SFAs; saturated fat from the FFQ if exposure from the FFQ), baseline Hb A_{1c} value, and the duration between baseline and follow-up Hb A_{1c} assessments. Exposures from the FFQ were adjusted for caloric intake and physical activity. The vitamin D model was further adjusted for BMI *z* score and the season in which samples were collected. The sample size varies by exposure and model covariates, ranging from $n = 435$ in model 2 for FFQ exposures, which were measured only in children aged ≥10 y, to $n = 807$ in model 1 for vitamin D. FFQ, food-frequency questionnaire; Hb A_{1c}, glycated hemoglobin; SNAS, SEARCH Nutrition Ancillary Study; 25(OH)D, 25-hydroxyvitamin D.

DISCUSSION

Our findings suggest that nutritional factors such as n–3 fatty acids, particularly EPA, and nutrients, particularly carbohydrates, protein, and leucine, may be significantly associated with Hb A_{1c} over a period of about 2 y after the clinical diagnosis of T1D in youth. These findings are particularly important because of poor dietary habits in the population of youth with diabetes compared with in the general youth population (18), which ultimately intensifies the risk of early life, aggressive microvascular and macrovascular complications (19).

A few published studies suggested associations of breastfeeding and the introduction of solid food with β cell autoimmunity and development of T1D, particularly in individuals at increased genetic risk of T1D (6, 8). In this study, we showed no significant association of infant feeding exposures such as breastfeeding and the timing of introduction of complimentary foods with Hb A_{1c}. It is possible that these early nutritional factors play an important role in the pathophysiology of development of T1D but may be less influential during the progression of extant T1D.

Increased intake of long-chain n–3 fatty acids may reduce risk of the development of islet autoimmunity and risk of T1D as well as improve glycemic control, possibly through their anti-inflammatory effects (9, 20–24) or other aspects of glucose transport (25). Our finding of the inverse association of the n–3 fatty acid EPA with follow-up Hb A_{1c} supports the beneficial effects of long-chain fatty acids on Hb A_{1c} in youth recently diagnosed with T1D. We also recently reported that this nutritional exposure was associated with sustained β cell function after the clinical diagnosis of T1D (11). The active form of vitamin D enhances insulin-mediated glucose transport (26). In addition, vitamin D receptors are expressed in skeletal and adipose tissue (27), which are the main sites of peripheral glucose uptake. A study in individuals with T1D showed that the repletion of vitamin D in deficient individuals improved Hb A_{1c} (10). We showed that higher baseline vitamin D intake was significantly associated with lower follow-up Hb A_{1c} but only in the partially adjusted model, and in the SEARCH study, we previously showed no association between vitamin D status and insulin sensitivity (28). It is possible that the null prospective association observed for vitamin D in the fully adjusted model was due to our inability to measure the active form of vitamin D3, 1α,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], vitamin D receptors, or vitamin D receptor genes, which can directly influence glucose transport and uptake and ultimately influence glycemic control. Vitamin E, particularly α-tocopherol, has been suggested to reduce oxidative stress and decrease blood glucose concentrations through improved insulin secretion, thereby

lowering Hb A_{1c} (29). However, in our study, vitamin E intake was not significantly associated with follow-up Hb A_{1c}. A similar nonsignificant association was reported for β cell function in this cohort (11), and thus, it is unlikely that vitamin E enhances glycemic control in this population of youth with T1D.

Carbohydrate intake is one of the primary determinants of postprandial glucose concentrations and, therefore, may influence glycemic control (30). The findings from our longitudinal analyses suggested that increased total carbohydrate intake is associated with increased Hb A_{1c}, similar to the results of a large European cross-sectional study (31). There has been an increased interest in the role of dietary fiber in the management of diabetes and its complications. A few studies showed that fiber intake was associated with improved daily blood glucose concentration or long-term glycemic control represented by Hb A_{1c} (32–34). However, our study showed no evidence of an association between fiber intake and Hb A_{1c}, which was consistent with findings from the Diabetes Control and Complications trial (35). Our study population of youth with T1D had substantially lower fiber intakes relative to the American Diabetes Association recommendation of 14 g/1000 kcal (36). It is possible that the low fiber intake in this population may not have been sufficient to influence Hb A_{1c}.

The consumption of higher- compared with lower-fat meals (with similar carbohydrate and protein amounts) in T1D adults has been suggested to increase blood glucose concentrations and insulin requirements (37). In addition, in the Diabetes Control and Complications trial, a diet higher in fat and saturated fat was associated with worse Hb A_{1c} (35). In contrast, metabolic studies suggested that higher-fat diets that contained a greater proportion of unsaturated fat may rather result in better glucose metabolism than does a high-carbohydrate diet (38). Our study showed that higher baseline fat intake was marginally associated with lower follow-up Hb A_{1c} only in the partially adjusted model.

Dietary protein and leucine intakes can stimulate insulin secretion (39, 40). Animal studies also suggested an improved glucose concentration and Hb A_{1c} because of protein or leucine supplementation (41, 42). A beneficial effect of leucine on the preservation of β cell function was recently reported in this cohort (11). Our study findings also suggested that increased intakes of protein and leucine are associated with better Hb A_{1c}. Leucine supplementation was previously suggested to increase postprandial insulin secretion and insulin response (41). In addition, leucine supplementation may significantly decrease adipose tissue inflammation and, thus, lead to improved glucose metabolism (41). More studies are required to explore and confirm the beneficial role of leucine intake on Hb A_{1c}.

A few strengths of this study are worth mentioning. We used data from a large cohort of youth with well-characterized T1D to assess the prospective associations of nutritional factors with Hb A_{1c}. Most previous research that assessed the roles of nutritional factors on Hb A_{1c} have assessed only one dietary exposure and used cross-sectional designs. To our knowledge, our study is the first to assess the relations of various types of nutritional exposures with Hb A_{1c} in the high-risk group of youth with T1D. Current research findings in this area have been dominated by findings in type 2 diabetes populations, which have limited generalizability to T1D populations.

Our study had a few limitations. Nutritional exposure data including infant feeding exposures and baseline dietary intakes from the FFQ relied on a retrospective self-report and, therefore, may have been prone to error. In addition, nutritional exposure data were available only for the baseline visit, and we assumed that diet remained unchanged over the period of 1–2 y. Data on longitudinal changes in diet in T1D youth are lacking. A study from Finland (43) showed that diet quality decreased over the 24-mo period after diagnosis in youth with T1D. However, a previous analysis of our study population showed no significant change in diet quality by using the Dietary Approaches to Stop Hypertension index over the 5-y period after diagnosis (44). Hence, our assumption of little to no dietary change over the 2-y period after diagnosis is relevant. Moreover, if the quality of diet in our population had decreased as reported in the aforementioned Finnish study (43), our point estimates would have been attenuated toward the null because of underestimation. Our study considered Hb A_{1c} as a marker of long-term glycemic control. The findings may not applicable to the issue of prevention or treatment of short-term hypoglycemia or hyperglycemia. We did not have data on daily glucose measures to capture day-to-day glycemic fluctuations, which have recently been suggested as a strong predictor of overall glycemic control (45). Future studies are needed to explore the relations of nutritional exposures with short-term glycemia. This analysis was not within the scope of our study. Our study explored the associations between nutritional exposures and Hb A_{1c} in youth with an early age at the onset of diabetes. Future studies should explore whether these nutritional effects are consistent across different ages of onset and disease durations.

In conclusion, several nutritional factors may influence Hb A_{1c} after the clinical diagnosis of T1D in youth. In addition to the overall role of major macronutrients such as carbohydrate and protein, leucine and n–3 fatty acid intake, such as of EPA, may significantly affect Hb A_{1c}. These findings inform nutrition intervention strategies in terms of usual dietary patterns particularly during the early disease-progression period and complement strategies focusing on an insulin regimen for the management of day-to-day glycemia. Findings regarding increased carbohydrate intake related to increased Hb A_{1c} in this population of youth with T1D speak to the need for continuous education on carbohydrate portioning and distribution and insulin-to-carbohydrate management. Findings can be used to design future studies to assess the efficacy of nutritional approaches for long-term glycemic control in youth diagnosed with T1D.

The authors' responsibilities were as follows—APL: contributed to the concept development, designed the research, provided consultation for the data analysis, and wrote the manuscript; EJM-D: conceptualized the study, designed the research, provided scientific input, provided consultation for data analysis, and reviewed and edited the manuscript; JLC: performed data management, analyzed data, assisted in the interpretation of results, and reviewed and edited the manuscript; LMJ, SCC, and JML: provided scientific input, assisted in the interpretation of results, and reviewed and edited the manuscript; APL and EJM-D: were guarantors of this work and, as such, had full access to all data in the study and took responsibility for the integrity of data and accuracy of the data analysis; and all authors: read and approved

the final manuscript. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. Diabetes Care 2004;27:955–62.
2. Cleary PA, Orchard TJ, Genuth S, Wong ND, Detrano R, Backlund JY, Zinman B, Jacobson A, Sun W, Lachin JM, et al. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes 2006;55:3556–65.
3. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, Lachin JM, Polonsky KS, Pozzilli P, Skyler JS, et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. Diabetes 2004;53:250–64.
4. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003;26:832–6.
5. Petitti DB, Klingensmith GJ, Bell RA, Andrews JS, Dabelea D, Imperatore G, Marcovina S, Pihoker C, Standiford D, Waitzfelder B, et al. Glycemic control in youth with diabetes: the SEARCH for diabetes in Youth Study. J Pediatr 2009;155:668–72.
6. Kimpimäki T, Erkkola M, Korhonen S, Kupila A, Virtanen SM, Ilonen J, Simell O, Knip M. Short-term exclusive breastfeeding predisposes young children with increased genetic risk of Type I diabetes to progressive beta-cell autoimmunity. Diabetologia 2001;44:63–9.
7. Virtanen SM, Knip M. Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age. Am J Clin Nutr 2003;78:1053–67.
8. Frederiksen B, Kroehl M, Lamb MM, Seifert J, Barriga K, Eisenbarth GS, Rewers M, Norris JM. Infant exposures and development of type 1 diabetes mellitus: The Diabetes Autoimmunity Study in the Young (DAISY). JAMA Pediatr 2013;167:808–15.
9. Stene LC, Joner G. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr 2003;78:1128–34.
10. Aljabri KS, Bokhari SA, Khan MJ. Glycemic changes after vitamin D supplementation in patients with type 1 diabetes mellitus and vitamin D deficiency. Ann Saudi Med 2010;30:454–8.
11. Mayer-Davis EJ, Dabelea D, Crandell JL, Crume T, D'Agostino RB Jr., Dolan L, King IB, Lawrence JM, Norris JM, Pihoker C, et al. Nutritional factors and preservation of C-peptide in youth with recently diagnosed type 1 diabetes: SEARCH Nutrition Ancillary Study. Diabetes Care 2013;36:1842–50.
12. American Diabetes Association. Standards of medical care in diabetes-2014. Diabetes Care 2014;37:S14–80.
13. SEARCH Study Group. SEARCH for Diabetes in Youth: a multicenter study of the prevalence, incidence and classification of diabetes mellitus in youth. Control Clin Trials 2004;25:458–71.
14. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11 2002;246:1–190.
15. Liese A, Crandell JL, Tooze JA, Fangman MT, Couch S, Merchant AT, Bell R, Mayer-Davis EJ. Relative validity and reproducibility of FFQ in youth with type 1 diabetes. Public Health Nutr 2014;18:428–37.
16. Kostraba JN, Cruickshanks KJ, Lawler-Heavner J, Jobim LF, Rewers MJ, Gay EC, Chase HP, Klingensmith G, Hamman RF. Early exposure to cow's milk and solid foods in infancy, genetic predisposition, and risk of IDDM. Diabetes 1993;42:288–95.
17. Lemaitre RN, King IB, Patterson RE, Psaty BM, Kestin M, Heckbert SR. Assessment of trans-fatty acid intake with a food frequency questionnaire and validation with adipose tissue levels of trans-fatty acids. Am J Epidemiol 1998;148:1085–93.
18. Mayer-Davis EJ, Nichols M, Liese AD, Bell RA, Dabelea DM, Johansen JM, Pihoker C, Rodriguez BL, Thomas J, Williams D. Dietary intake among youth with diabetes: the SEARCH for Diabetes in Youth Study. J Am Diet Assoc 2006;106:689–97.
19. Sochett E, Daneman D. Early diabetes-related complications in children and adolescents with type 1 diabetes. Implications for screening and intervention. Endocrinol Metab Clin North Am 1999;28:865–82.
20. Norris JM, Yin X, Lamb MM, Barriga K, Seifert J, Hoffman M, Orton HD, Baron AE, Clare-Salzler M, Chase HP, et al. Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA 2007;298:1420–8.
21. Miller MR, Yin X, Seifert J, Clare-Salzler M, Eisenbarth GS, Rewers M, Norris JM. Erythrocyte membrane omega-3 fatty acid levels and omega-3 fatty acid intake are not associated with conversion to type 1 diabetes in children with islet autoimmunity: the Diabetes Autoimmunity Study in the Young (DAISY). Pediatr Diabetes 2011;12:669–75.
22. Julius U. Fat modification in the diabetes diet. Exp Clin Endocrinol Diabetes 2003;111:60–5.
23. Müllner E, Plasser E, Brath H, Waldschutz W, Forster E, Kundi M, Wagner KH. Impact of polyunsaturated vegetable oils on adiponectin levels, glycaemia and blood lipids in individuals with type 2 diabetes: a randomised, double-blind intervention study. J Hum Nutr Diet 2014;27:468–78.
24. Udupa A, Nahar P, Shah S, Kshirsagar M, Ghongane B. A comparative study of effects of omega-3 Fatty acids, alpha lipoic Acid and vitamin e in type 2 diabetes mellitus. Ann Med Health Sci Res 2013;3:442–6.
25. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 2006;7:85–96.
26. Maestro B, Campion J, Davila N, Calle C. Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocr J 2000;47:383–91.
27. Cândido FG, Bressan J. Vitamin D: link between osteoporosis, obesity, and diabetes? Int J Mol Sci 2014;15:6569–91.
28. The NS, Crandell JL, Lawrence JM, King IB, Dabelea D, Marcovina SM, D'Agostino RB Jr., Norris JM, Pihoker C, Mayer-Davis EJ. Vitamin D in youth with Type 1 diabetes: prevalence of insufficiency and association with insulin resistance in the SEARCH Nutrition Ancillary Study. Diabet Med 2013;30:1324–32.
29. Ihara Y, Yamada Y, Toyokuni S, Miyawaki K, Ban N, Adachi T, Kuroe A, Iwakura T, Kubota A, Hiai H, et al. Antioxidant alpha-tocopherol ameliorates glycemic control of GK rats, a model of type 2 diabetes. FEBS Lett 2000;473:24–6.
30. Franz MJ, Powers MA, Leontos C, Holzmeister LA, Kulkarni K, Monk A, Wedel N, Gradwell E. The evidence for medical nutrition therapy for type 1 and type 2 diabetes in adults. J Am Diet Assoc 2010;110:1852–89.
31. Buyken AE, Toeller M, Heitkamp G, Irsigler K, Holler C, Santeusanio F, Stehle P, Fuller JH. Carbohydrate sources and glycaemic control in Type 1 diabetes mellitus. EURODIAB IDDM Complications Study Group. Diabet Med 2000;17:351–9.
32. Giacco R, Parillo M, Rivellese AA, Lasorella G, Giacco A, D'Episcopo L, Riccardi G. Long-term dietary treatment with increased amounts of fiber-rich low-glycemic index natural foods improves blood glucose control and reduces the number of hypoglycemic events in type 1 diabetic patients. Diabetes Care 2000;23:1461–6.
33. Toeller M. Fibre consumption, metabolic effects and prevention of complications in diabetic patients: epidemiological evidence. Dig Liver Dis 2002;34(Suppl 2):S145–9.
34. Rovner AJ, Nansel TR, Gellar L. The effect of a low-glycemic diet vs a standard diet on blood glucose levels and macronutrient intake in children with type 1 diabetes. J Am Diet Assoc 2009;109:303–7.
35. Delahanty LM, Nathan DM, Lachin JM, Hu FB, Cleary PA, Ziegler GK, Wylie-Rosett J, Wexler DJ. Association of diet with glycated hemoglobin during intensive treatment of type 1 diabetes in the Diabetes Control and Complications Trial. Am J Clin Nutr 2009;89:518–24.
36. American Diabetes Association, Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, et al. Nutrition recommendations and interventions for diabetes: A position statement of American Diabetes Association. Diabetes Care 2008;31:S61–78.

37. Wolpert HA, Atakov-Castillo A, Smith SA, Steil GM.. Dietary fat acutely increases glucose concentrations and insulin requirements in patients with type 1 diabetes: implications for carbohydrate-based bolus dose calculation and intensive diabetes management. Diabetes Care 2013;36:810–6.
38. Lichtenstein AH, Schwab US. Relationship of dietary fat to glucose metabolism. Atherosclerosis 2000;150:227–43.
39. Yang J, Chi Y, Burkhardt BR, Guan Y, Wolf BA. Leucine metabolism in regulation of insulin secretion from pancreatic beta cells. Nutr Rev 2010;68:270–9.
40. Dämon S, Schatzer M, Hofler J, Tomasec G, Hoppichler S. Nutrition and diabetes mellitus: an overview of the current evidence. Wien Med Wochenschr 2011;161:282–8.
41. Guo K, Yu YH, Hou J, Zhang Y. Chronic leucine supplementation improves glycemic control in etiologically distinct mouse models of obesity and diabetes mellitus. Nutr Metab (Lond) 2010;7:57–67.
42. Gaudel C, Nongonierma AB, Maher S, Flynn S, Krause M, Murray BA, Kelly PM, Baird AW, FitzGerald RJ, Newsholme P. A whey protein hydrolysate promotes insulinotropic activity in a clonal pancreatic beta-cell line and enhances glycemic function in ob/ob mice. J Nutr 2013;143:1109–14.
43. Virtanen SM, Ylonen K, Rasanen L, la-Venna E, Maenpaa J, Akerblom HK. Two year prospective dietary survey of newly diagnosed children with diabetes aged less than 6 years. Arch Dis Child 2000;82:21–6.
44. Barnes TL, Crandell JL, Bell RA, Mayer-Davis EJ, Dabelea D, Liese AD. Change in DASH diet score and cardiovascular risk factors in youth with type 1 and type 2 diabetes mellitus: The SEARCH for Diabetes in Youth Study. Nutr Diabetes 2013;3:e91.
45. Sartore G, Chilelli NC, Burlina S, Di SP, Piarulli F, Fedele D, Mosca A, Lapolla A. The importance of HbA1c and glucose variability in patients with type 1 and type 2 diabetes: outcome of continuous glucose monitoring (CGM). Acta Diabetol 2012;49(Suppl 1):S153–60.