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Dietary Quality and Markers of Inflammation: No Association in Youth with Type 1 Diabetes in the SEARCH for Diabetes in Youth Study

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Abstract

Background—Systemic inflammation is a key process underlying cardiovascular disease (CVD) development, and CVD risk is significantly elevated in persons with type 1 diabetes (T1D). Youth with T1D exhibit increased levels of inflammation. Studies in persons without diabetes suggest that dietary quality influences inflammation, yet little is known about dietary influences on inflammation in youth with T1D.

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Conflicts of interest: None.

Methods—This study evaluated the association of four distinct dietary quality indices (Dietary Approaches to Stop Hypertension (DASH), Healthy Eating Index 2010 (HEI2010), modified KIDMED and Total Antioxidant Capacity (TAC)) with biomarkers of inflammation (C-reactive protein (CRP), fibrinogen and interleukin-6 (IL-6)) in a sample of 2,520 youth with T1D participating in the SEARCH for Diabetes in Youth Study.

Results—Average diet quality was moderate to poor, with mean scores of 43 (DASH, range 0–80), 55 (HEI2010, range 0–100), 3.7 (mKIDMED, range 3–12) and 7237 (TAC). None of the four diet quality scores was associated with the selected biomarkers of inflammation in any analyses. Evaluation of a non-linear relationship or interactions with BMI or levels of glycemic control did not alter the findings. Replication of analyses using longitudinal data yielded consistent findings with our cross-sectional results.

Conclusions—Biomarkers of inflammation in youth with T1D may not be directly influenced by dietary intake, at least at the levels of dietary quality observed here. More work is needed to understand what physiologic mechanisms specific to persons with T1D might inhibit the generally beneficial influence of high dietary quality on systemic inflammation observed in populations without diabetes.

Keywords

Diet quality; inflammation; youth; type 1 diabetes mellitus

1. Introduction

Autoimmune, insulin-dependent diabetes mellitus (type 1 diabetes, T1D) is one of the leading chronic diseases of childhood and adolescence, and its prevalence is increasing worldwide.[1–4] Despite improvements in T1D treatment, the trends for its associated cardiovascular complications have not improved. Persons with T1D have a more than three-fold higher risk of acute cardiovascular disease (CVD) compared to persons without diabetes, resulting in a lower life expectancy of roughly seven years.[5–7]

Systemic inflammation is a key process underlying the development of CVD.[8] The SEARCH for Diabetes in Youth Case Control Study has shown that youth with T1D exhibit increased inflammation compared to youth without diabetes, independent of obesity.[9] Moreover, higher levels of the inflammation biomarkers fibrinogen, C-reactive protein (CRP) and interleukin-6 (IL-6) are associated with a more atherogenic lipid profile among youth with T1D.[8,10] CRP and fibrinogen are both acute-phase proteins indicative of systemic inflammation, with fibrinogen also being a marker of hemostasis and a pro-thrombotic state.[11] IL-6 is a proinflammatory cytokine.[11] Thus, there is an urgent need to identify mechanisms to reduce systemic inflammation among youth with T1D.

Because dietary intake is known to influence inflammation in the general population, modifying intake of specific nutrients or foods may be a promising approach to reduce inflammation in youth with T1D, assuming that these relationships are similar across populations.[12] Many of the common components in a Western diet pattern are linked to pro-inflammatory mechanisms, whereas anti-inflammatory attributes characterize

Mediterranean-style and Asian diets.[12] Moreover, several studies have shown that high-quality dietary intake, characterized using the Dietary Approaches to Stop Hypertension (DASH) index,[13] the Healthy Eating Index (HEI)[14,15] and the Mediterranean Diet Index, have higher anti-inflammatory potential.[16,17] A dietary score has also been developed that focuses specifically on the total antioxidant capacity (TAC) of a diet.[18,19] In addition, there is evidence from experimental studies for the pro-inflammatory effects of high fat, high carbohydrate and high glycemic index meals. (NEW REFS Campbell et al 2014, Ghanim et al 2007, Ghanim et al 2009) Given the relationship between oxidative stress and inflammation, higher total antioxidant capacity of a diet may be associated with lower levels of inflammation. To date, higher TAC scores have been associated with decreased incidence of heart failure, myocardial infarction and stroke but have not been explored with respect to inflammatory markers.[20,21]

This study examines the association between four dietary quality indices—DASH,[13] mKIDMED[22] (a version of the Mediterranean diet score modified to be applicable to children), HEI2010 and TAC—and three inflammation markers—fibrinogen, CRP and IL-6—using data from the SEARCH Air Pollution and Inflammation Ancillary Study and the SEARCH for Diabetes in Youth Nutrition Ancillary Study.[23]

2. Material and Methods

The SEARCH for Diabetes in Youth study is an ongoing multicenter study of physician-diagnosed diabetes mellitus in youth younger than age 20 at diagnosis that began in 2001.[24,25] The study was approved by the local Institutional Review Boards. Data collection sites were located in South Carolina, Ohio, Colorado, Washington and Southern California. Parents of participants under age 18 provided written informed consent with participant assent; all participants aged 18 years or older provided written informed consent at each visit.

2.1 Study participants

The current analysis is restricted to youth whose diabetes was prevalent in 2001 or incident between 2002 and 2005 that completed a SEARCH study visit (n=5,079; 63% of 8,031 ascertained by the SEARCH surveillance system/registry). We limited the analysis to individuals with T1D (n=4,468) age 10 or older (n=2,943) at the time of their visit because dietary intake was not collected in those younger than 10 years. We then excluded those with a missing food frequency questionnaire (FFQ, n=423), leaving 2,520 youth with dietary intake data for descriptive analyses. Among those youth, 670 had missing data on fibrinogen, thus the analysis for fibrinogen is based on 1,850 youth, and the analysis for CRP is based on 1,847. The analyses of IL-6 are based on 1,329 youth.

2.2 Inflammation markers

Levels of the inflammatory biomarkers fibrinogen, CRP and IL-6 were measured in plasma samples after an eight-hour fast. Specimens were processed at the sites and shipped within 24 hours to the Northwest Lipid Metabolism and Diabetes Research Laboratories in Seattle, Washington. Levels of CRP and fibrinogen were determined using Siemens reagent on a

Siemens BNII nephelometer autoanalyzer (Siemens Healthcare Diagnostics Inc., Newark, Delaware). Levels of IL-6 were measured by Multiplex bead technology using an adipokine-B panel (Linco Research, Inc., now EMD Millipore. Inc.) on a BioRad Bioplex analyzer.

2.3 Diet assessment and dietary indices

Four dietary indices were used to evaluate diet quality in this study; DASH, HEI2010, mKIDMED and TAC. All indices were coded based on food item, food group and nutrient data from the SEARCH FFQ. The diet assessment protocol has been described in detail elsewhere.[23] In brief, the FFQ consisted of 85 food lines (i.e. questions about one or multiple foods or beverages being consumed) for which the participant indicated whether the item was consumed in the past week ("yes/no") and if yes, how many days and the average portion size. Portion size was queried for each line item as a number or as "very small," "small," "medium" or "large" relative to pictures of food. A final open-ended question queried all other foods that a participant might want to report. The FFQ was primarily self-administered after staff instruction.

Food groups were created by either collapsing food lines based on their major components or by disaggregating composite foods into basic foods. The dietary intake data were collected and analyzed using Nutrition Data System for Research (NDSR 2014) developed by the Nutrition Coordinating Center (NCC) at the University of Minnesota, Minneapolis, MN. The SEARCH FFQ was recently validated and has been shown to have reasonable characteristics for the majority of food groups and nutrients used in this analysis.[26]

Adherence to the DASH diet was assessed with an index (i.e., score) variable based on the algorithms developed by Günther et al,[27] resulting in an overall DASH adherence score that ranged from 0 to 80. The HEI2010 score was calculated following the method described by the National Cancer Institute,[14,15] resulting in an overall HEI2010 that ranged from 0 to 100.[28,29] Details of the mKIDMED score have also been described.[22,30–32] In brief, this score aims to characterize the degree to which dietary intake in children or adolescents resembles a Mediterranean diet. Items denoting a negative connotation with respect to a Mediterranean diet were assigned a value of −1, whereas those with a positive aspect were scored +1, yielding a total range of 3 to 12. The TAC was calculated from the FFQ using a database of the most common foods in the United States analyzed with the oxygen radical absorbance capacity (ORAC) assay.[18,19] ORAC measures the antioxidant capacity of a food item to reduce free radicals, taking into account the synergism between compounds. To calculate the total antioxidant capacity of a person's diet, the average frequency of consumption of each food was multiplied by the ORAC values (μmol Trolox [Hoffman-LaRoche, Basel, Switzerland] Equivalents (TE)/100 g). The ORAC was adjusted for energy intake using the residual method.

2.4 Covariates

Covariates included age at study visit, gender, race and ethnicity, study site, duration of T1D, body mass index (BMI), smoking status, physical activity, family income, parental education and A1c level at the study visit. Race and ethnicity were obtained through self-report using standard Census questions.[33] Physical examinations at the study visits were

conducted according to standardized protocols by trained and certified staff. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated as weight (kg)/height squared (m^2) and converted to a BMI z-score.[34] Physical activity was assessed using questions identical to or slightly modified from the Youth Risk Behavior Surveillance System (YRBS).[35,36] Smoking, family income and parental education were based on self-report. A1c was measured by a dedicated ion exchange high performance liquid chromatography instrument (TOSOH, Bioscience, Inc., San Francisco, CA).

2.5 Statistical analysis

Mean intake of food groups, energy and nutrients were compared among tertiles of dietary indices using analysis of variance (ANOVA). Correlations of food groups and dietary indices were assessed using Spearman's correlation test. Variables with skewed distribution (fibrinogen, CRP, IL-6) were log-transformed prior to use in statistical models. A series of multivariable linear regression models were fit, first unadjusted (Model 1) and then adjusted for sociodemographic (non-modifiable) confounders (age, gender, race and ethnicity, study site, T1D duration, Model 2) and subsequently for modifiable risk factors (smoking status, physical activity, family income, parental education, Model 3) followed by addition of BMI Z-score (Model 4). A1c was included in the final models as a potential mediator (Model 5). A limited number of interaction models were tested as part of sensitivity analyses. P-values <0.05 were considered significant. An additional analysis was conducted on a subset of participants (N=518) with longitudinal measurements of three of the four diet quality indices (DASH, HEI2010, and mKIDMED), plus fibrinogen and CRP. Multiple regression models of change in diet scores predicting change in inflammation over time were utilized to assess the association between change in diet quality and change in inflammation in these individuals. Statistical analyses were conducted using SAS (version 9.3, SAS Institute Inc, Cary, NC).

3. Results

Characteristics of the study sample are shown in Table 1. The average age was approximately 14 years, with an equal distribution between females and males. The majority were non-Hispanic white, and the average diabetes duration was 53 months (~4.5 years). Mean levels were 359.8 mg/dl for fibrinogen (SD 69.8), 0.2 mg/dl for CRP (SD 0.4) and 18.2 pg/ml for IL-6 (SD 24.2) on the untransformed scales. Dietary intake quality was on average moderate, with a mean DASH score of 43 (out of 80), mean HEI2010 of 55 (out of 100), mean mKIDMED of 3.7 (out of 15) and mean TAC of 7237 μmol TE/100 grams.

Table 2 further illustrates the distribution of food group intake, dietary index scores and inflammatory markers in our study population. Although not all of the score components are represented here, the ones chosen offer a comparison between the indices. In addition, we computed Pearson's correlations between the four dietary quality scores and found strong correlations between DASH and HEI2010 ($r_{DASH\text{-}HEI2010}=0.63$), moderate correlations between HEI2010, mKIDMED and TAC ($r_{HEI2010\text{-}mKIDMED}=0.52$; $r_{HEI2010\text{-}TAC}=0.50$; $r_{mKIDMED\text{-}TAC}=0.51$) and lower correlations between DASH and mKIDMED and TAC ($r_{DASH\text{-}mKIDMED}=0.39$ and $r_{DASH\text{-}TAC}=0.38$).

As shown in Table 3, in unadjusted linear regression models (Model 1), none of the four indices of diet quality were associated with fibrinogen, CRP or IL-6. When adjusted for sociodemographic variables (Model 2), neither BMI nor A1c (Model 3) altered these findings. Additional analyses exploring a potential non-linear relationship of the dietary quality indices with biomarkers of inflammation, an interaction with BMI and an interaction with levels of glycemic control did not offer new insights, and the findings remained unchanged (data not shown). Longitudinal measurements of diet, fibrinogen and CRP were available on a subset of participants (N=518). Regression models assessed the association between change in diet quality (DASH, HEI2010, and mKIDMED) and change in inflammation; the findings were unchanged from the cross-sectional models. Finally, analyses were repeated as longitudinal models in a smaller data set (N=518), and again, the findings were unchanged.

4. Discussion

Given our previous findings that a high-quality diet characterized by DASH score is strongly related to more favorable anthropometric measures, lipid levels and better glycemic control in youth with T1D and that adherence to a Mediterranean diet is associated with better glycemic control and lipid levels,[13,22,27,37] the present paper was motivated by the question of which of these dietary indices—if adhered to—has the greatest potential to reduce systemic inflammation in youth with T1D. Contrary to expectations, our study did not find evidence for an association of the quality of dietary intake and biomarkers of systemic inflammation. Although this finding contrasts with studies conducted in populations without diabetes,[16,38–45] it mirrors the null findings we reported previously[46] on the association of fiber intake and markers of inflammation in the same study population. Given the correlation between dietary quality indices and fiber intake ($r_{DASH\text{-}Fiber}$=0.20; $r_{HEI2010\text{-}Fiber}$=0.34; $r_{mKIDMED\text{-}Fiber}$=0.58, $r_{TAC\text{-}Fiber}$=0.64), this consistency is reassuring. One hypothesis that could explain the null findings that we put forth previously[46] is that the “dose” of the healthful dietary exposure observed in our population is significantly lower than recommended. Mean levels of DASH, HEI2010 and mKIDMED scores were at the midpoint of the respective score’s range, intake at the 75th percentile still fell short of recommended levels, and no one in our study population approached a diet that was consistent with recommended intake levels. Another potential explanation could be related to differences in the populations studied, considering that the majority of published data on dietary quality and inflammation were obtained in persons without diabetes.[16,38–45] Jaacks et al. (2014) speculated that given the higher levels of systemic inflammation typically observed in youth with T1D compared to youth without diabetes, “…in this study population there are factors with stronger causal effects on inflammation … and this may mask any beneficial effects [of diet].”[46]

One such potentially stronger influence may be the gut microbiome, which is situated along the causal pathway between dietary intake and inflammation. Persons with T1D differ from those without diabetes in terms of the types and abundance of gut microbiota.[47–51] Bacteria producing lactate and butyrate may play an important role because butyrate is conducive to the health of gut epithelial cells and seems to have anti-inflammatory properties.[47,50] Thus, it is conceivable that the dysregulated gut microbiome in T1D may render potentially

beneficial healthy dietary intake constituents less effective in reducing systemic inflammation. This line of reasoning was recently advanced as a potential explanation for the inconsistent effects of breast milk consumption on risk of autoimmunity development in the pathogenesis of T1D.[52]

In further support of our null findings is the fact that each of the four dietary quality indices was unrelated to biomarkers of inflammation. There is substantial overlap among the components of the DASH, HEI2010 and mKIDMED indices, as all three place emphasis on fruits, vegetables, dairy products and grains/cereals and discourage sweets/empty calories. The main foods and beverages contributing to variability in FFQ-based TAC levels are also consistent with those of the aforementioned indices, namely fruit and vegetables, grain products, juice, chocolate and tea (and wine in adult populations). However, there are also notable differences related to sodium and fatty acid (in the HEI2010), and the consideration of fast food intake is unique to the mKIDMED index; hence, the correlations between the four indices ranged from moderate to strong (r=0.38–0.63).

The TAC score is a novel dietary quality index in that it focuses on the antioxidant capacity of foods.[18,21] The FFQ-based TAC score has been validated against plasma TAC levels and has additionally shown excellent reliability on repeat administration of the FFQ.[18] Furthermore, high dietary TAC scores have been associated with reduced risk of myocardial infarction, stroke, heart failure and cataract in adults, which are all influenced by underlying inflammation.[19,53–55] Antioxidants scavenge circulating reactive oxygen species and reactive nitrogen species,[56] thereby buffering against oxidative stress and in turn promoting increased endothelial health. In addition, fruit and vegetables are high in flavonoids, which have anti-inflammatory and anti-coagulation effects.[57]

There are a number of limitations and strengths to the present study. Among the limitations is the fact that this was a cross-sectional analysis, which limits causal inference; however, repeating the analyses in a smaller longitudinal sample (N= 518 confirmed the null associations. Furthermore, given that methodology to control for measurement error is still evolving for dietary quality indices, this study, unlike others we have published,[26,46] did not control for measurement error in dietary intake. Our study was limited to existing data, and we had access to only three biomarkers of inflammation (CRP, fibrinogen, and IL-6). Given how many other inflammatory markers are known to exist (e.g., TNF-alpha, IL-18, etc.) and may be associated with dietary intake, the three biomarkers available to us may constitute a poor representation of the comprehensive manner in which inflammation and oxidative stress can be measured with more contemporary markers.[11] Thus, our conclusions are not definitive, and future studies may benefit from including additional inflammation markers that may help explain the association of dietary intake with inflammation. Among the strengths is that we used four different measures of dietary quality rather than focusing on a single dietary index.

Furthermore, in the literature on dietary influences on systemic inflammation among T1D, only one previous publication focused on dietary patterns measuring dietary quality.[58] In a population of adults in their mid-forties with T1D, Ahola *et al.* found that adherence to dietary recommendations for select food groups (e.g., fish, fresh and cooked vegetables,

cooked vegetables, fruits and berries, soft drinks, sweet pastry, candy, low-fat liquid milk products, etc.) was associated with decreased high-sensitivity CRP in men but not in women.[58] Our findings did not offer support for this type of association, as there was no evidence for an interaction with gender (data not shown).

5. Conclusions

In conclusion, given the lack of an association between dietary quality and inflammation in youth with T1D, future research may consider characterizing attributes that are along the causal pathway between dietary intake and inflammation, including the gut environment.

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Table 1

Demographic and clinical characteristics of youth with type 1 diabetes aged 10 years or older participating in the SEARCH Air Pollution and SEARCH Nutrition Ancillary Studies (n=2,520)[1]

Variables	Mean (SD) or Percentage
Age, years	14.2 (3.0)
Diabetes duration, months	52.9 (50.4)
Gender	
Female	50.6
Male	49.4
Race	
Non-Hispanic white	77.7
Black	8.5
Others	13.8
Household income	
<$25k	11.8
$25k–$49k	20.1
$50k–$74k	20.3
≥$75k	39.6
Don’t know/missing	8.2
Parental education	
Less than high school	4.1
High school graduate	15.8
Some college or associate degree	32.6
Bachelor degree or more	47.5
Current Smoking	
Yes	21.4
No	78.6
Physical activity	
0–2 days	38.6
3–7 days	61.4
BMI z-score	0.6 (0.9)
A1c	8.2 (1.7)
Study site	
SC	11.8
OH	21.4
CO	29.4
CA	13.2
WA	24.3
DASH score (range 0 to 80)	42.8 (9.1)
HEI2010 score (range 0 to 100)	55.0 (10.7)
mKIDMED score (range −3 to 12)	3.7 (1.9)
TAC, μmol TE/100 g	7236.9 (4986.5)

Variables	Mean (SD) or Percentage
Inflammation markers	
Fibrinogen, mg/dl	359.8 (69.8)
C-reactive protein, mg/dl	0.2 (0.4)
IL-6, pg/ml	18.2 (24.2)

[1] All dietary data are based on n=2,520; fibrinogen is based on n=1,850; C-reactive protein is based on n=1,847; and IL-6 is based on n=1,329.

Table 2

Descriptive characteristics of key food groups, dietary indices and markers of inflammation in youth with type 1 diabetes aged 10 years or older in the SEARCH Air Pollution and SEARCH Nutrition Ancillary Studies[1]

	Mean	SD	Minimum	25th	Median	75th	Maximum
Food group (servings/1,000 kcal)							
Total grains	2.1	0.7	0.0	1.6	2.0	2.4	5.8
High-fiber grains	0.1	0.1	0.0	0.0	0.0	0.0	1.2
Vegetables	0.9	0.7	0.0	0.5	0.8	1.2	10.1
Fruit	0.7	0.5	0.0	0.3	0.6	0.9	4.1
Total dairy	1.1	0.7	0.0	0.6	0.9	1.4	6.5
Low-fat dairy	0.8	0.6	0.0	0.3	0.6	1.1	6.5
Meat	0.8	0.5	0.0	0.5	0.7	1.0	5.4
Nuts & seeds	0.6	1.0	0.0	0.0	0.2	0.8	7.4
Fats & oils	1.5	1.0	0.0	0.8	1.3	1.9	7.5
Sweets	0.8	0.5	0.0	0.4	0.7	1.0	3.6
Dietary index							
DASH score (range 0 to 80)	42.8	9.1	7.7	36.7	43.1	49.1	71.3
HEI2010 score (range 0 to 100)	55.0	10.7	21.9	47.4	54.9	62.3	93.1
mKIDMED score (range −3 to 12)	3.7	1.9	−1.0	2.0	4.0	5.0	11.0
TAC, μmol TE/100 g	7236.9	4986.5	22.9	3785.4	6125.9	9374.6	58159.8
Inflammation markers							
Fibrinogen, mg/dl	359.8	69.8	230.0	311.0	350.0	398.0	799.0
C-reactive protein, mg/dl	0.2	0.4	0.0	0.0	0.1	0.2	2.4
IL-6, pg/ml	18.2	24.2	0.1	3.8	9.3	22.0	232.1

[1]All dietary data are based on n=2,520; fibrinogen is based on n=1,850; C-reactive protein is based on n=1,847; and IL-6 is based on n=1,329.

Table 3

Association of DASH, HEI2010, mKIDMED and TAC scores with markers of inflammation in youth with type 1 diabetes aged 10 years or older in the SEARCH Air Pollution and SEARCH Nutrition Ancillary Studies

	DASH			HEI2010			mKIDMED			TAC		
	beta[a]	SE	p	beta[a]	SE	p	beta[a]	SE	p	Beta[b]	SE	p
Fibrinogen[C], mgdl (n=1,850)												
Model 1	−0.031	0.048	0.52	0.00	0.041	0.93	0.182	0.228	0.43	0.002	0.126	0.99
Model 2	0.018	0.048	0.71	−0.01	0.040	0.90	0.202	0.223	0.37	−0.077	0.123	0.53
Model 3	0.033	0.050	0.50	0.0003	0.041	0.99	0.233	0.227	0.30	−0.006	0.124	0.96
Model 4	0.041	0.049	0.40	−0.006	0.040	0.88	0.176	0.223	0.43	0.019	0.121	0.88
Model 5	0.066	0.048	0.16	0.006	0.039	0.87	0.209	0.218	0.34	0.080	0.119	0.50
C-reactive protein[C], mgdl (n=1,847)												
Model 1	−0.616	0.370	0.10	−0.088	0.312	0.78	2.300	1.748	0.19	−0.338	0.966	0.73
Model 2	−0.189	0.358	0.60	−0.192	0.299	0.52	1.142	1.667	0.49	−0.761	0.917	0.41
Model 3	0.053	0.372	0.89	−0.060	0.308	0.85	1.494	1.695	0.38	−0.203	0.930	0.83
Model 4	0.130	0.350	0.71	−0.110	0.289	0.70	1.205	1.600	0.45	0.047	0.874	0.96
Model 5	0.267	0.347	0.44	−0.034	0.287	0.91	1.502	1.585	0.34	0.366	0.865	0.67
IL-6[C]pg/ml, (n=1,329)												
Model 1	0.577	0.382	0.13	0.137	0.321	0.67	−0.713	1.806	0.69	−0.876	1.008	0.39
Model 2	0.447	0.390	0.25	0.077	0.325	0.81	−1.076	1.809	0.55	−0.836	1.009	0.41
Model 3	0.372	0.407	0.36	−0.000	0.337	1.00	−1.353	1.859	0.47	−0.805	1.026	0.43
Model 4	0.350	0.409	0.39	−0.063	0.339	0.85	−1.535	1.863	0.41	−0.883	1.027	0.39
Model 5	0.399	0.411	0.33	−0.033	0.340	0.92	−1.441	1.873	0.44	−0.866	1.028	0.40

[a]: beta for 100 unit dietary indexes increase.

[b]: beta for 100,000 unit TAC increase.

[c]: log transformed.

Model 1: Unadjusted;

Model 2: Adjusted for age, gender, race, site, duration;

Model 3: Adjusted for age, gender, race, site, duration, smoke, physical activity, income, parental education;

Model 4: Adjusted for age, gender, race, site, duration, BMI-z, smoke, physical activity, income, parental education;

Model 5: Adjusted for age, gender, race, site, duration, BMI-z, smoke, physical activity, income, parental education, A1C level.

Bold: $p<0.05$.