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Association between Plasma trans-Fatty Acid Concentrations and Diabetes in a Nationally Representative Sample of U.S. Adults

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Abstract

Background—High *trans* fatty acid (TFA) diet induces insulin resistance in experimental studies in rodent models and primates. However, previous epidemiological studies on the association between *trans* fatty acids (TFAs), mainly based on self-reported intake from diet, and diabetes

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have yielded conflicting results. We examined the associations of objectively-measured plasma TFA concentrations with diabetes in a large population-based study among U.S. adults.

Methods—We included 3,801 participants aged 20 years or older from the National Health and Nutrition Examination Survey 1999–2000 and 2009–2010. Four major TFAs, including palmitelaidic acid (C16:1n-7t), elaidic acid (C18:1n-9t), vaccenic acid (C18:1n-7t), and linolelaidic acid (C18:2n-6t, 9t), were measured in fasting plasma using gas chromatography-mass spectrometry. Diabetes was defined by self-reported physician diagnosis, plasma fasting glucose ≥ 126 mg/dL, or glycated hemoglobin (HbA1c) $\geq 6.5\%$.

Results—After adjustment for other major risk factors, the odds ratio (OR) of diabetes comparing the highest with lowest quintile of plasma TFAs was 2.19 (95% CI, 1.27–3.79) for total TFAs (P for trend 0.01), 2.34 (1.48–3.72) for elaidic acid (P for trend 0.0004), 1.33 (0.82–2.15) for linolelaidic acid (P for trend 0.18), 1.58 (0.97–2.58) for palmitelaidic acid (P for trend 0.02), and 1.64 (0.95–2.84) for vaccenic acid (P for trend 0.09). In addition, total TFAs, elaidic acid, palmitelaidic acid, and vaccenic acid were significantly associated with fasting glucose, fasting insulin, insulin resistance index, and HbA1c.

Conclusions—In a nationally representative population, plasma TFAs, in particular elaidic acid, were positively associated with diabetes and biomarkers of glucose metabolism.

Keywords

trans-fatty acid; elaidic acid; palmitelaidic acid; vaccenic acid; linolelaidic acid; diabetes; nutrition; human health

Introduction

Trans Fatty acids (TFAs) are fatty acids with at least one non-conjugated double bond in the *trans* configuration.¹ In the past, TFAs, mainly from the partial hydrogenation of vegetable oils, were widely used in the food industry, and although their use is declining, TFAs are still found in some processed foods today.² Humans could also ingest TFAs in a small amount from dairy products and meats.³ Since 2005, the Dietary Guidelines for Americans have recommended reducing TFA consumption to as low as possible.⁴ Under concerns of the adverse health effects of TFAs, the Food and Drug Administration (FDA) published a final rule, effective January 1, 2006, to require that nutrition labels for all conventional foods and supplements must indicate the contents of TFAs.⁵ In 2015, the FDA released a final determination that partially hydrogenated oils are not “generally recognized as safe” for use in food and requested the food companies to eliminate them from food in three years.⁶ These measures have led to significantly reduced plasma TFA levels in U.S. population.^{6, 7}

TFAs have attracted critical attention as a potential modifiable risk factor for diabetes.⁸ Diabetes is a worldwide public health issue due to its severe complications and increasing prevalence.⁹ Previous studies about associations between TFAs and diabetes have yielded conflicting results.^{10, 11} For example, Papantoniou et al found that TFA intake was not associated with diabetes,¹⁰ while Salmeron et al found a positive and significant association with diabetes.¹¹ These inconsistencies may be due in part to the use of dietary questionnaires, which are subject to measurement errors caused by recall bias and inaccurate

estimation. Therefore, studies using TFA biomarkers that provide more objective and reliable measure of TFA status are needed. So far, only a few studies have examined the associations between circulating TFA isomers and diabetes yielding inconsistent findings.^{12–16} Moreover, biological samples in those studies were collected before 2006, so associations between TFA biomarkers and diabetes after the sharp drop in TFA exposure after 2006 are not known.^{7, 17} In addition, those studies were conducted in middle age or older adults. No information about young adults has been reported.

In this study, we examined the associations of plasma concentrations of total TFAs and individual TFA isomers with diabetes and diabetic biomarkers in a wide age range using data from nationally representative surveys.

Methods

Study population

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey of the non-institutionalized U.S. population. It is administered by the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC). NHANES collects data on demographics, socioeconomic status, lifestyle, diet, and medical conditions, as well as specimens for laboratory tests, which are publicly released in 2-year cycles. Detailed descriptions of NHANES are available elsewhere.¹⁸ NHANES has been approved by the National Center for Health Statistics Ethics Review Board. Written informed consent was obtained from all participants.

For this analysis, we used data from NHANES 1999–2000 and 2009–2010, because only these two cycles included available data on plasma TFA concentrations.⁷ Of the 20,502 participants in NHANES 1999–2000 and 2009–2010, plasma TFAs were measured in a fasting morning samples of 4,029 adults aged 20 years and older. Individuals with missing information on total blood lipids ($n = 47$) were excluded, because TFA was adjusted for total blood lipids as recommended.¹⁹ Pregnant women ($n = 114$) and individuals who had cardiovascular disease prior to diagnosis of diabetes ($n = 38$) were excluded from analysis. Moreover, given that body mass index (BMI) is an important confounder of the association between TFA and diabetes²⁰ and that only 0.8% of individuals ($n = 29$) had missing data on BMI, we excluded those individuals without BMI data. The final sample consisted of 3,801 participants (48% men, aged 50.1 ± 17.9 ; 52% women, aged 50.0 ± 17.8) (see electronic supplementary material [ESM] Figure. 1).

Exposure assessment

Four major TFA isomers, including palmitelaidic acid (C16:1n-7t), elaidic acid (C18:1n-9t), vaccenic acid (C18:1n-7t), and linolelaidic acid (C18:2n-6t, 9t), were measured in fasting plasma samples using gas chromatography-mass spectrometry, at the Division of Laboratory Sciences, National Center for Environmental Health, CDC.²¹ These TFA isomers are the most abundant circulating TFA isomers and provide a reasonable representation of TFAs in blood.¹⁷ Total TFAs were calculated as the sum of these four TFA isomers.

The instrument details have been described elsewhere.²¹ The lower limits of detection (LLOD) are 0.07 umol/L for palmitelaidic, 0.28 umol/L for elaidic acid, 0.43 umol/L for vaccenic acid, and 0.02 umol/L for linolelaidic acid. The detection limits were constant for all of the analytes in the data set. All the measured TFA levels were at or above the LLOD. All TFA isomers were expressed as relative values (umol/g lipids) by dividing their concentrations with total blood lipids as recommended.¹⁹

Outcome ascertainment

Diabetes was defined based on self-reported physician diagnosis, plasma fasting glucose level of 126 mg/dL or more, or hemoglobin A1c (HbA1c) of 6.5% or more.²² Trained interviewers collected information on self-reported diabetes diagnosis using a Computer-Assisted Personal Interview system. HbA1c levels, plasma fasting glucose, and fasting insulin were measured from blood specimens collected during the exam and then later analyzed by an accredited laboratory using a standardized protocol.^{23, 24} Insulin resistance index was evaluated based on the updated homeostasis model of assessment (HOMA2-IR).²⁵

Potential confounders

Information on age, gender, race/ethnicity, family income, education, smoking status, medical conditions, and family history of diabetes was collected during the NHANES in-person home-interviews. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican American, and other race/ethnicity (other race and other Hispanic). Education was grouped as less than high school, high school, and higher than high school (including some college or associates (AA) degree, college graduate or higher). Family income-to-poverty ratios were categorized as 1.30, 1.31–3.50, and > 3.50.²⁶ Individuals who smoked less than 100 cigarettes in their lifetime were defined as never smokers; those who had smoked more than 100 cigarettes but did not smoke at the time of survey were considered former smokers; those who had smoked more than 100 cigarettes and smoked cigarettes at the time of survey were current smokers.²⁷ Validity of self-reported smoking in NHANES was confirmed by an objectively-measured biomarker in a previous study, with 96% of self-reported smokers having serum cotinine levels ≥ 3 ng/mL and 91% of self-reported non-smokers (either never smokers or former smokers) having serum cotinine levels < 3 ng/mL.²⁸ Dietary information was collected through 24-hour dietary recall interviews. Total energy intake was calculated using the United States Department of Agriculture Automated Multiple-Pass Method.²⁹ Alcohol intake was categorized as 0 g/day, 0.1–28 g/day, ≥ 28 g/day for men, and 0 g/day, 0.1–14 g/d, ≥ 14 g/d for women. We classified physical activity into three groups (below: < 600 metabolic equivalent of task [MET] minutes/week or 150 minutes moderate-intensity /week; meet: 600–1200 MET minutes/week or 150–300 minutes/week; or exceed: >1200 MET minutes/week or 300 minutes/week) according to standards appropriate for each cycle,^{30, 31} because there were some changes in physical activity questionnaires between NHANES 1999–2000 and 2009–2010. Weight, height, and blood pressure were measured by trained health technicians. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2 , < 25, 25–29.9, ≥ 30). The 2010 healthy eating index (HEI-2010) score was calculated to represent diet quality, with a higher score indicating a better diet.³²

Statistical analysis

NHANES used a complex, multistage probability sampling design to represent the civilian non-institutionalized U.S. population. Weighted estimates were used to adjust for the differential probability of selection and non-response. Because TFA was measured on a fasting morning sample, the fasting sample weights were used in the analyses. The Taylor series linearization method was applied for variance estimation to account for stratification and clustering, following the NHANES Analytic Guidelines.²⁶ Plasma TFA concentrations were log-transformed prior to analysis because of skewed distributions. We used analysis of variance to compare differences of total calories intake, alcohol intake, and HEI score among quintiles of plasma *trans* fatty acids. We applied Chi-square test to compare distribution of categorical variables, such as sex, race/ethnicity, and education levels, among quintiles of plasma *trans* fatty acids. Pearson correlations with sample weights were used to calculate correlation coefficients among concentrations of each TFA isomer. Logistic regression was used to estimate the odds ratios (ORs) of diabetes according to quintiles of plasma TFA concentrations. Among individuals without diabetes, linear regression was used to estimate the association between TFAs and glucose metabolism biomarkers including fasting glucose, fasting insulin, HOMA2-IR, and HbA1c. We adjusted for a number of potential confounders in our analysis including age, gender, race/ethnicity, and survey cycle (Model 1); and additional adjustment for education, family income-to-poverty ratios, smoking status, alcohol intake, total energy intake, physical activity, family history of diabetes, and HEI-2010 (Model 2). In Model 3, we additionally adjusted for BMI because it might be a confounder or mediator of the associations between plasma TFAs and diabetes.^{20, 33} Categorical covariates included a subgroup for missing data, if necessary. To test linear trends across quintiles of TFA concentrations, we assigned the median for each quintile and fitted the log-transformed median as a continuous variable in models. We also repeated the analyses in each survey cycle (1999–2000, 2009–2010) separately.

To evaluate effect modification, we conducted stratified analyses according to age (20–49, 50 years), gender (men, women), and race/ethnicity (non-Hispanic White, other racial/ethnic groups). P values for heterogeneity were derived from the multiplicative interaction term coefficients (exposure variable $\times$ effect modifier variable) added to the main effects multivariable model.

To detect the robust of our findings, we conducted a sensitivity analysis by excluding individuals who reported only insulin use, a rough indicator of type 1 diabetes.³⁴

All statistical analyses were performed using SAS version 9.4 (SAS Institute). Statistical significance was set at the 0.05 level.

Results

The median plasma concentration for total TFAs was 8.17 $\mu\text{mol/g}$ lipids (interquartile range [IQR], 5.64–12.41), for elaidic acid was 3.08 $\mu\text{mol/g}$ lipids (IQR, 2.00–4.97), for linolelaidic acid was 0.63 $\mu\text{mol/g}$ lipids (IQR, 0.43–0.94), for palmitelaidic acid was 0.77 $\mu\text{mol/g}$ lipids (IQR, 0.58–1.07), and for vaccenic acid was 3.96 $\mu\text{mol/g}$ lipids (IQR, 2.70–6.06). Higher levels of plasma total TFA were found among non-Hispanic whites, and those with lower

education level, lower physical activity, or higher BMI, and those with family history of diabetes (Table 1). Characteristics of participants of each TFA isomer are shown in Table S1–S4. The four isomers were highly correlated with each other; correlation coefficients ranged from 0.79 to 0.93 (all P values < 0.001). Plasma concentrations of total plasma TFAs and each TFA isomer according to population characteristics are shown in Table S5.

Association between TFAs and diabetes

We found a significant association between plasma total TFAs and diabetes. After adjustment for demographic, socioeconomic, lifestyle, dietary factors, and family history of diabetes, the OR of diabetes for total TFA levels, comparing the highest quintile to lowest, was 2.19 (95% confidence interval [CI], 1.27–3.79; P for trend 0.01) (Table 2). The association was modestly attenuated, but remained significant after additional adjustment for BMI (OR 1.83, 95% CI, 1.04–3.21; P for trend 0.056). We also examined the association between each TFA isomer and the presence of diabetes. The multivariable-adjusted OR of diabetes for elaidic acid, comparing the highest quintile to lowest, was 2.34 (95% CI, 1.48–3.72; P for trend 0.0004), for linolelaidic acid was 1.33 (95% CI, 0.82–2.15; P for trend 0.18), for palmitelaidic acid was 1.58 (95% CI, 0.97–2.58; P for trend 0.02), and for vaccenic acid was 1.64 (95% CI, 0.95–2.84; P for trend 0.08) (Table 2). When we simultaneously included the four TFA isomers in the same multivariable model, significant associations were only found between elaidic acid and diabetes (OR 3.27, 95% CI 1.64–6.51; P for trend 0.001). The observed associations did not differ significantly by age, gender, or race/ethnicity (Table S6–S8).

To learn whether the associations between TFAs and diabetes change after the reduction of TFA levels, we examined the associations between TFAs and diabetes in each survey cycle. In NHANES 1999–2000, we found significant associations between total plasma TFAs and diabetes (P for trend 0.03). The multivariable adjusted OR for diabetes, compared the highest with lowest quintile, was 2.54 (95% CI, 1.07–6.03) (Table 3). In NHANES 2009–2010, the association was attenuated, with corresponding OR of 1.59 (95% CI, 0.94–2.68; P for trend 0.06) (Table 4). For individual TFA isomers, only elaidic acid was significantly associated with diabetes in both cycles (NHANES 1999–2000: OR 3.73, 95% CI 1.29–10.81, P for trend 0.01; NHANES 2009–2010: OR 2.28, 95% CI 1.46–3.54, P for trend 0.01).

Association between TFAs and glucose metabolism biomarkers

We found significant associations between total plasma TFAs and glucose metabolism biomarkers in adults without diabetes. In the multivariable-adjusted model, plasma total TFA concentration was significantly associated with fasting glucose (P for trend 0.007), fasting insulin (P for trend < 0.001), HOMA2-IR (P for trend < 0.001), and HbA1c (P for trend 0.003) (Table 5). Analyses of individual TFA isomers showed a significant association of glucose metabolism biomarkers with elaidic acid, vaccenic acid, and palmitelaidic acid, but not linolelaidic acid (Table 5).

Discussion

To our knowledge, this is the first study that comprehensively examined the association between plasma concentrations of the four major TFA isomers and diabetes. In this nationally representative population, higher plasma concentrations of total TFAs, in particular elaidic acid, were positively and significantly associated with diabetes in U.S. adults, even after adjustment for other risk factors. In adults without diabetes, total TFAs, elaidic acid, palmitelaidic acid, and vaccenic acid were positively associated with biomarkers of altered glucose metabolism.

The association between total TFA concentrations, which were objectively-measured in plasma samples, and diabetes was consistent with several previous studies linking dietary TFA intake based on dietary questionnaires to diabetes. Higher dietary TFA intake has been associated with diabetes,¹¹ insulin sensitivity,³⁵ and systemic inflammation.³⁶ Animal studies have found that a high TFA diet induces significant insulin resistance in mice³⁷ and causes weight gain and impaired insulin sensitivity in monkeys.³⁸ In vivo and in vitro studies found that TFAs can inhibit the expression of peroxisome proliferator-activated receptor γ , which plays an important role in glucose metabolism.³⁹ Other underlying mechanisms may include the effects on liver X receptor and sterol regulatory element-binding protein-1.¹

Effects of specific TFA isomers on the development of diabetes remain to be determined. Previous studies have yielded inconsistent findings, which may be partly due to the different ways to estimate specific TFA exposure, either based on dietary questionnaires¹¹ or measurements in blood samples.¹⁵ Studies examining the associations of selected individual blood TFA isomers with diabetes are sparse, and the TFA isomers measured in previous studies varied. Wang et al used data from the Cardiovascular Health Study and found that phospholipid *trans*-16:1n-9 and *trans*-18:1 were positively associated with diabetes among older adults.¹³ Mozaffarian et al found that *trans*-palmitelaidic acid was associated with a lower risk of diabetes in U.S. adults,^{14, 15} while a Finnish study showed that neither *trans*-palmitelaidic acid nor elaidic acid were significantly associated with diabetes.¹² In a previous study among Chinese adults examining the associations between erythrocytes fatty acids and multiple cardiometabolic traits, erythrocyte *trans*-18:1 fatty acid, but not *trans*-18:2 fatty acid, was associated with a lower risk of type 2 diabetes.^{16, 40} As previous studies suggested,⁴¹ the sources of various *trans*-18:1 isomers may be quite different: *trans*-18:1

4- 10 mainly come from industrial products while *trans*-18:1 11 comes from ruminants. In the present study, we found that *trans*-18:1 isomers 11 (i.e., 18:1n-7t) showed a weaker association with diabetes than *trans*-18:1 isomers 9 (i.e., 18:1n-9t). This was in line with existing evidence indicating less adverse effects of ruminant TFA compared to industrial TFAs on cardiometabolic health.⁴² Other factors, including study design, population characteristics, and confounders, may contribute to the inconsistent findings on associations of TFAs with diabetes. Importantly, the timeframe in which these studies were conducted might be an important factor. In the U.S., several FDA policies and dietary guidelines were published in 2006 to call for a limited intake of TFAs, which did cause a sharp decrease of human exposure to TFAs.⁷ The blood samples in all above-mentioned U.S. studies were collected before 2006,¹³⁻¹⁵ while the circulating TFA levels in China¹⁶ and Finland¹² were

lower than that in the U.S. and the range is relatively narrower. The relatively smaller range of TFA levels of these previous studies in comparison to our current analysis may limit the ability to detect a difference in the risk of diabetes. In addition, dairy products, the main sources of palmitelaidic acid and vaccenic acid, also contain other bioactive nutrients (i.e., vitamin D, calcium, magnesium, casein, and whey protein) at different amounts. Because these nutrients may contribute to a lower risk of diabetes,⁴³ they could mask the potential adverse effects of TFAs on diabetes.⁴³ Clearly, further investigation is warranted to clarify the association between specific TFA isomers and diabetes.

Consistent with findings between plasma TFA concentrations and diabetes, we observed positive and significant associations between some plasma TFAs and fasting glucose, fasting insulin, HOMA2-IR, and HbA1c, in adults without diabetes. Similar findings were observed in the study by Itcho et al, in which serum elaidic acid concentrations were associated with insulin resistance.⁴⁴ Angelieri et al. also reported detrimental effects of TFA intake on insulin sensitivity.³⁵

A major strength of our study is a broader range of TFA levels compared to that of previous studies. The geometric means of total TFAs in NHANES 1999–2000 was 81.4 umol/L and 37.8 umol/L in NHANES 2009–2010, representing a 54% decrease of plasma TFA concentrations between these two cycles.^{7, 26} Taking advantage of data from these two survey cycles, which provided a larger range of TFA levels, could increase the ability to detect associations between TFAs and diabetes.¹ This is supported by our analysis in specific survey cycles. We did not find significant associations between palmitelaidic acid and diabetes in NHANES 1999–2000 or NHANES 2009–2010, respectively, which is consistent with previous studies.¹² However, the association between palmitelaidic acid and diabetes turned out to be significant when merging these two cycles together.

This study has other strengths as well. First, to our knowledge, this is the first study that comprehensively examined the association between plasma concentrations of TFAs and diabetes in a nationally representative study in the U.S., which allows for better generalizability of our findings to a broader population. Second, plasma TFAs isomers were directly measured, which is more reliable and not subject to recall bias as seen in previous questionnaire-based studies.⁴⁵ Third, this study provides new data in the general population by including all adults aged 20 years or older, as opposed to only older adults as previously studied.^{12, 13} Finally, glucose metabolism biomarkers, such as fasting glucose and HbA1c, were measured in a large sample size to support our findings on diabetes. As expected, we observed consistent results for the associations of plasma TFAs with diabetes and glucose metabolism biomarkers.

We acknowledge that there are also some limitations in this study. First, due to the cross-sectional nature of NHANES, we cannot draw a causal inference from the observed associations. Second, NHANES did not provide sufficient data to distinguish type 1 diabetes and type 2 diabetes. However, the results were robust when we excluded individuals who reported only insulin use, a rough indicator of type 1 diabetes.³⁴ Third, the NHANES did not measure total plasma TFA directly. Instead, total TFA was calculated using the four major TFA isomers that are the most abundant in blood samples. Summing of these four major

TFA isomers have been used in previous studies to estimate total TFA concentration in US population.⁷ Fourth, although many potential confounders were adjusted for, we cannot rule out the possibility of residual confounding by unknown factors.

In conclusion, in this nationally representative study, we found significant associations of plasma concentrations of total TFAs, in particular elaidic acid, with diabetes and glucose metabolism biomarkers in US adults. Our results support the US federal regulation on reducing TFA intake in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Comprehensively examined the association between plasma concentrations of the four major TFA isomers and diabetes.
- Taking advantage of data from two NHANES cycles provided a larger range of TFA levels, which increases the ability to detect associations between TFAs and diabetes.
- Higher plasma concentrations of total TFAs, in particular elaidic acid, were associated with diabetes in U.S. adults.
- In adults without diabetes, total TFAs, elaidic acid, palmitelaidic acid, and vaccenic acid were positively associated with biomarkers of altered glucose metabolism.

Table 1

Characteristics of participants aged 20 years and over by quintiles of plasma concentrations of total *trans* fatty acids from NHANES 1999–2000 and NHANES 2009–2010

Characteristics	Quintiles of plasma concentration of total <i>trans</i> fatty acids					P
	Quintile 1 <5.1 umol/g lipids	Quintile 2 5.1–6.8 umol/g lipids	Quintile 3 6.8–9.0 umol/g lipids	Quintile 4 9.0–12.7 umol/g lipids	Quintile 5 >12.7 umol/g lipids	
Number of participants	760	760	761	760	760	
Age, years	45.7 ± 0.8	45.4±0.8	47.3±0.9	47.0±1.0	44.9±0.8	0.43
Sex, %						
Men	52.3 (1.8)	47.0 (2.5)	52.6 (2.1)	47.8 (1.8)	46.4 (2.7)	0.19
Women	47.7 (1.8)	53.0 (2.5)	47.4 (2.1)	52.2 (1.8)	53.6 (2.7)	
Race/ethnicity, %						
Non-Hispanic whites	57.7 (3.7)	67.1 (3.2)	70.2 (3.8)	75.1 (3.0)	80.0 (2.0)	<0.001
Non-Hispanic black	13.4 (1.3)	12.9 (1.3)	8.6 (1.3)	8.8 (1.5)	7.6 (1.8)	
Mexican American	7.8 (1.1)	7.8 (2.0)	9.7 (2.2)	7.6 (1.7)	6.3 (1.3)	
Other race/ethnicity	21.1 (3.6)	12.2 (2.4)	11.5 (3.2)	8.5 (2.3)	6.1 (1.5)	
Education, %						
Less than high school	17.8 (1.7)	19.1 (2.3)	21.0 (1.8)	23.8 (1.7)	21.9 (1.5)	<0.001
High school	17.8 (2.3)	19.8 (1.8)	26.5 (2.3)	28.2 (2.7)	30.0 (3.4)	
College or higher	64.4 (2.4)	61.1 (2.5)	52.5 (3.2)	48.0 (2.8)	48.1 (3.5)	
Family income to poverty ratio, %						
1.30	18.1 (1.2)	20.0 (1.7)	19.3 (2.0)	20.7 (2.7)	18.4 (2.5)	0.92
1.31–3.50	32.4 (2.3)	32.6 (1.6)	36.7 (2.9)	32.9 (2.5)	35.5 (2.7)	
>3.50	41.3 (2.4)	40.0 (2.2)	36.2 (3.1)	38.7 (2.9)	38.3 (3.7)	
Missing	8.2 (1.5)	7.7 (1.3)	7.8 (1.4)	7.7 (1.3)	7.8 (1.6)	
Smoking, %						
Never smoker	56.9 (3.4)	56.7 (2.4)	49.1 (2.8)	52.2 (3.6)	47.7 (2.7)	0.14
Current smoker	17.8 (2.0)	22.4 (2.2)	21.2 (2.0)	22.3 (3.5)	24.2 (2.3)	
Ever smoker	25.3 (2.7)	20.9 (2.0)	30.0 (2.9)	25.5 (2.4)	28.1 (2.2)	
Total calories, kcal/d	2111.7 ± 50.6	2212.6±10.1	2207.1±37.7	2237.7±43.8	2256.6±29.4	0.33
Alcohol intake, g/d	14.6±1.5	12.2±1.4	12.5±1.3	9.4±1.0	6.0±0.8	0.73

Characteristics	Quintiles of plasma concentration of total <i>trans</i> fatty acids					P
	Quintile 1 <5.1 umol/g lipids	Quintile 2 5.1–6.8 umol/g lipids	Quintile 3 6.8–9.0 umol/g lipids	Quintile 4 9.0–12.7 umol/g lipids	Quintile 5 >12.7 umol/g lipids	
Physical activity [*] , %						
Below	31.8 (2.9)	35.7 (1.7)	41.6 (2.2)	42.1 (3.1)	39.3 (2.7)	
Meet	13.0 (1.5)	10.4 (1.3)	13.1 (1.5)	12.4 (1.5)	16.2 (1.9)	0.01
Exceed	55.2 (3.2)	53.9 (2.2)	45.3 (2.2)	45.5 (3.1)	44.6 (3.2)	
HEI	54.8±0.8	49.9±0.7	48.7±0.8	46.2±0.9	42.6±0.8	0.13
BMI, %						
<25 kg/m ²	42.4 (2.8)	28.4 (1.7)	33.5 (2.1)	34.7 (1.9)	35.1 (2.5)	
25–29.9 kg/m ²	32.4 (2.4)	34.7 (2.0)	33.5 (1.9)	33.3 (2.7)	28.4 (1.8)	0.003
30 kg/m ²	25.2 (2.4)	36.9 (2.1)	33.0 (1.9)	32.0 (2.1)	36.5 (2.6)	
Family history of diabetes, %						
Yes	31.7 (1.9)	36.6 (2.0)	41.4 (2.6)	46.2 (2.3)	49.2 (3.1)	
No	66.4 (1.7)	61.5 (2.2)	57.1 (2.7)	51.3 (2.2)	49.3 (2.7)	<0.001
Missing	1.9 (0.6)	1.9 (0.5)	1.5 (0.5)	2.5 (0.9)	1.5 (0.7)	

Values were weighted means ± standard errors for continuous variables and weighted percentages (standard errors) for categorical variables, except the number of participants.

* Physical activity was classified as below, meet or exceed the recommended level of the 2008 Physical Activity Guidelines for Americans.

Table 2 Associations of plasma concentrations of *trans* fatty acids with diabetes in U.S. adults (N = 3,801)

	Quintiles of plasma concentrations of <i>trans</i> fatty acids					P for trend	OR per unit
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Total <i>trans</i> fatty acids							
Median, umol/g lipids	4.1	5.9	7.8	10.7	16.3		
No. of diabetes cases	84	106	116	102	97		
OR (95% CI)							
Model 1	1 [Ref]	1.42 (1.05–1.93) *	1.74 (1.17–2.57)	1.98 (1.33–2.94)	2.64 (1.48–4.72)	0.001	2.01 (1.34–3.00)
Model 2	1 [Ref]	1.33 (1.01–1.75)	1.43 (0.91–2.25)	1.57 (1.01–2.42)	2.19 (1.27–3.79)	0.01	1.71 (1.13–2.59)
Model 3	1 [Ref]	1.18 (0.88–1.57)	1.30 (0.84–2.00)	1.29 (0.82–2.04)	1.83 (1.04–3.21)	0.056	1.51 (0.99–2.29)
Elaidic acid							
Median, umol/g lipids	1.4	2.1	2.9	4.3	6.8		
No. of diabetes cases	81	95	123	110	96		
OR (95% CI)							
Model 1	1 [Ref]	1.17 (0.79–1.73)	1.72 (1.21–2.45)	2.22 (1.47–3.35)	3.00 (1.84–4.85)	<0.001	2.11 (1.52–2.92)
Model 2	1 [Ref]	1.04 (0.74–1.48)	1.42 (0.96–2.11)	1.70 (1.10–2.64)	2.34 (1.48–3.72)	0.0004	1.79 (1.30–2.48)
Model 3	1 [Ref]	0.99 (0.69–1.43)	1.25 (0.84–1.87)	1.41 (0.88–2.26)	1.96 (1.22–3.13)	0.007	1.58 (1.14–2.20)
Linolelaidic acid							
Median, umol/g lipids	0.3	0.4	0.6	0.8	1.3		
No. of diabetes cases	100	108	116	101	80		
OR (95% CI)							
Model 1	1 [Ref]	1.19 (0.79–1.79)	1.49 (0.95–2.35)	1.43 (0.93–2.19)	1.43 (0.85–2.41)	0.08	1.30 (0.97–1.75)
Model 2	1 [Ref]	1.13 (0.77–1.67)	1.48 (0.92–2.40)	1.27 (0.82–1.96)	1.33 (0.82–2.15)	0.18	1.22 (0.91–1.64)
Model 3	1 [Ref]	1.10 (0.75–1.61)	1.48 (0.91–2.38)	1.28 (0.81–2.00)	1.38 (0.87–2.20)	0.09	1.27 (0.96–1.67)

Quintiles of plasma concentrations of <i>trans</i> fatty acids						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	OR per unit
Palmitelaidic acid						
Median, umol/g lipids	0.4	0.6	0.7	0.9	1.4	
No. of diabetes cases	88	98	96	126	97	
OR (95% CI)						
Model 1	1 [Ref]	1.26 (0.90–1.75)	1.17 (0.82–1.67)	2.23 (1.43–3.46)	2.05 (1.18–3.56)	0.002 2.06 (1.32–3.21)
Model 2	1 [Ref]	1.22 (0.83–1.78)	1.00 (0.66–1.50)	1.91 (1.19–3.06)	1.58 (0.97–2.58)	0.02 1.63 (1.08–2.44)
Model 3	1 [Ref]	1.09 (0.72–1.65)	0.82 (0.54–1.25)	1.54 (0.99–2.40)	1.29 (0.78–2.15)	0.14 1.37 (0.90–2.06)
Vaccenic acid						
Median, umol/g lipids	2.0	2.8	3.7	5.0	7.6	
No. of diabetes cases	89	123	93	114	86	
OR (95% CI)						
Model 1	1 [Ref]	1.61 (1.12–2.33)	1.24 (0.82–1.89)	2.06 (1.32–3.21)	1.87 (1.07–3.29)	0.01 1.57 (1.10–2.23)
Model 2	1 [Ref]	1.59 (1.13–2.24)	1.09 (0.69–1.73)	1.80 (1.15–2.82)	1.64 (0.95–2.84)	0.08 1.40 (0.96–2.03)
Model 3	1 [Ref]	1.47 (1.05–2.05)	1.07 (0.70–1.66)	1.61 (1.01–2.58)	1.61 (0.93–2.78)	0.09 1.37 (0.95–1.99)

* OR; 95% CI in parentheses (all such values).

Model 1: adjusted for age (in years), gender (men, women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other race/ethnicity), and survey cycle (NHANES 1999–2000 or 2009–2010).

Model 2: Model1 + education (less than high school, high school, college or higher), family income (family income to poverty ratio: 1.30, 1.31–3.50, > 3.50, or missing), cigarette smoking (never, past, current), physical activity (below, meet, exceed), alcohol intake (men: 0, 0.1–27.9 g/d, 28 g/d; women: 0, 0.1–13.9 g/d, 14 g/d), family history of diabetes (yes or no), total energy intake (quintiles), and HEI-2010 (quintiles).

Model 3: Model 2 + BMI (<25.0, 25.0–29.9, 30.0).

Table 3
Associations of plasma concentrations of *trans* fatty acids with diabetes in U.S. adults: NHANES 1999–2000

NHANES 1999–2000 (N=1,437)							
Variables	Quintiles of plasma concentrations of <i>trans</i> fatty acids					P for trend	OR per unit
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Total <i>trans</i> fatty acids							
Median, umol/g lipids	7.2	9.9	12.2	15.3	19.3		
No. of diabetes cases	22	31	28	26	35		
OR (95% CI)							
Model 1	1 [Ref]	1.66 (0.66–4.20) *	1.44 (0.60–3.46)	1.90 (0.59–6.15)	2.69 (1.00–7.26)	0.06	2.47 (0.97–6.27)
Model 2	1 [Ref]	1.26 (0.47–3.40)	1.20 (0.63–2.30)	1.58 (0.62–4.03)	2.54 (1.07–6.03)	0.02	2.54 (1.15–5.59)
Model 3	1 [Ref]	1.19 (0.45–3.14)	1.16 (0.64–2.10)	1.46 (0.58–3.68)	2.42 (1.04–5.63)	0.03	2.45 (1.10–5.44)
Elaidic acid							
Median, umol/g lipids	2.8	4.0	4.9	6.3	8.2		
No. of diabetes cases	21	29	26	27	39		
OR (95% CI)							
Model 1	1 [Ref]	1.70 (0.66–4.35)	1.34 (0.50–3.64)	1.53 (0.70–3.33)	3.44 (0.98–12.10)	0.054	2.82 (0.98–8.13)
Model 2	1 [Ref]	1.53 (0.62–3.79)	1.27 (0.61–2.64)	1.43 (0.70–2.94)	3.73 (1.29–10.81)	0.01	3.11 (1.25–7.69)
Model 3	1 [Ref]	1.39 (0.60–3.21)	1.16 (0.55–2.43)	1.28 (0.66–2.48)	3.43 (1.21–9.73)	0.02	2.97 (1.15–7.68)
Linolelaidic acid							
Median, umol/g lipids	0.5	0.7	0.9	1.1	1.5		
No. of diabetes cases	31	29	34	28	20		
OR (95% CI)							
Model 1	1 [Ref]	1.05 (0.44–2.50)	1.49 (0.64–3.44)	1.64 (0.63–4.529)	1.03 (0.38–2.80)	0.59	1.21 (0.57–2.56)
Model 2	1 [Ref]	0.83 (0.42–1.65)	1.29 (0.60–2.77)	1.37 (0.70–2.69)	1.08 (0.50–2.35)	0.46	1.26 (0.69–2.31)

Variables	NHANES 1999–2000 (N=1,437)					
	Quintiles of plasma concentrations of <i>trans</i> fatty acids					P for trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Model 3	1 [Ref]	0.86 (0.45–1.66)	1.26 (0.57–2.79)	1.39 (0.69–2.80)	1.20 (0.57–2.50)	0.35
Palmitelaidic acid						
Median, umol/g lipids	0.6	0.8	1.0	1.3	1.6	
No. of diabetes cases	23	29	30	27	33	
OR (95% CI)						
Model 1	1 [Ref]	2.04 (0.68–6.16)	1.85 (0.70–4.84)	1.90 (0.66–5.46)	2.20 (0.79–6.17)	0.20
Model 2	1 [Ref]	1.85 (0.63–5.45)	1.38 (0.51–3.74)	1.50 (0.53–4.23)	2.13 (0.82–5.53)	0.19
Model 3	1 [Ref]	1.82 (0.63–5.27)	1.32 (0.48–3.66)	1.39 (0.48–4.00)	2.00 (0.78–5.14)	0.26
Vaccenic acid						
Median, umol/g lipids	3.3	4.6	5.9	7.1	9.2	
No. of diabetes cases	26	29	31	25	32	
OR (95% CI)						
Model 1	1 [Ref]	1.80 (0.89–3.63)	1.32 (0.59–2.98)	1.95 (0.62–6.14)	1.86 (0.89–3.89)	0.19
Model 2	1 [Ref]	1.55 (0.74–3.23)	1.08 (0.60–1.92)	1.66 (0.64–4.30)	1.80 (0.99–3.28)	0.11
Model 3	1 [Ref]	1.62 (0.73–3.58)	0.97 (0.54–1.75)	1.68 (0.65–4.34)	1.79 (0.96–3.33)	0.13

* OR; 95% CI in parentheses (all such values).

Model 1: adjusted for age (in years), gender (men, women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other race/ethnicity).

Model 2: Model1 + education (less than high school, high school, college or higher), family income (family income to poverty ratio: 1.30, 1.31–3.50, > 3.50, or missing), cigarette smoking (never, past, current), physical activity (below, meet, exceed), alcohol intake (men: 0.1–27.9 g/d, 28 g/d; women: 0.1–13.9 g/d, 14 g/d), family history of diabetes (yes or no), total energy intake (quintiles), and HEI-2010 (quintiles).

Model 3: Model 2 + BMI (<25.0, 25.0–29.9, 30.0).

Table 4
Associations of plasma concentrations of *trans* fatty acids with diabetes in U.S. adults: NHANES 2009–2010

NHANES 2009–2010 (N=2,320)							
Variables	Quintiles of plasma concentrations of <i>trans</i> fatty acids					P for trend	OR per unit
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
Total <i>trans</i> fatty acids							
Median, umol/g lipids	3.8	5.0	6.0	7.5	10.1		
No. of diabetes cases	49	55	71	86	98		
OR (95% CI)							
Model 1	1 [Ref]	1.12 (0.57–2.21) *	1.46 (0.91–2.37)	1.93 (1.10–3.38)	1.93 (1.07–3.46)	0.006	2.10 (1.28–3.44)
Model 2	1 [Ref]	1.09 (0.63–1.88)	1.33 (0.87–2.04)	1.47 (0.93–2.33)	1.59 (0.94–2.68)	0.06	1.65 (0.99–2.74)
Model 3	1 [Ref]	0.96 (0.59–1.57)	1.11 (0.71–1.73)	1.28 (0.81–2.02)	1.24 (0.71–2.15)	0.30	1.32 (0.78–2.26)
Elaidic acid							
Median, umol/g lipids	1.3	1.7	2.2	2.8	4.0		
No. of diabetes cases	41	67	58	89	104		
OR (95% CI)							
Model 1	1 [Ref]	2.15 (1.45–3.20)	1.56 (1.06–2.30)	2.19 (1.54–3.11)	2.90 (1.83–4.60)	0.001	2.15 (1.45–3.20)
Model 2	1 [Ref]	2.00 (1.42–2.83)	1.39 (0.97–1.98)	1.74 (1.18–2.56)	2.28 (1.46–3.54)	0.006	1.74 (1.17–2.58)
Model 3	1 [Ref]	1.61 (1.04–2.50)	1.20 (0.80–1.80)	1.30 (0.81–2.10)	1.65 (0.99–2.73)	0.20	1.35 (0.86–2.12)
Linolelaidic acid							
Median, umol/g lipids	0.3	0.4	0.5	0.6	0.9		
No. of diabetes cases	54	76	62	87	80		
OR (95% CI)							
Model 1	1 [Ref]	1.81 (1.15–2.86)	1.59 (0.99–2.55)	2.06 (1.33–3.18)	1.82 (1.12–2.95)	0.008	1.55 (1.14–2.10)
Model 2	1 [Ref]	1.77 (1.19–2.63)	1.46 (0.92–2.32)	2.04 (1.32–3.15)	1.58 (0.98–2.55)	0.06	1.40 (0.99–1.97)

NHANES 2009–2010 (N=2,320)						
Variables	Quintiles of plasma concentrations of <i>trans</i> fatty acids					OR per unit
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
Model 3	1 [Ref]	1.63 (1.07–2.49)	1.35 (0.88–2.09)	2.00 (1.32–3.04)	1.55 (0.98–2.46)	0.03
Palmitelaidic acid						
Median, umol/g lipids	0.4	0.5	0.6	0.8	1.0	
No. of diabetes cases	54	57	69	74	105	
OR (95% CI)						
Model 1	1 [Ref]	1.35 (0.85–2.15)	1.49 (1.06–2.10)	1.59 (0.97–2.62)	2.16 (1.23–3.78)	0.02
Model 2	1 [Ref]	1.42 (0.94–2.13)	1.45 (0.91–2.30)	1.31 (0.75–2.28)	1.82 (1.04–3.16)	0.09
Model 3	1 [Ref]	1.14 (0.70–1.88)	1.19 (0.73–1.94)	0.93 (0.53–1.63)	1.28 (0.76–2.14)	0.59
Vaccenic acid						
Median, umol/g lipids	1.7	2.4	2.9	3.6	5.0	
No. of diabetes cases	56	55	88	70	90	
OR (95% CI)						
Model 1	1 [Ref]	0.97 (0.42–2.26)	1.97 (1.13–3.44)	1.27 (0.71–2.27)	1.71 (0.89–3.29)	0.05
Model 2	1 [Ref]	0.90 (0.39–2.07)	1.83 (1.12–2.98)	1.10 (0.63–1.91)	1.38 (0.74–2.60)	0.24
Model 3	1 [Ref]	0.80 (0.35–1.83)	1.54 (0.97–2.44)	1.06 (0.60–1.88)	1.19 (0.62–2.26)	0.46

* OR; 95% CI in parentheses (all such values).

Model 1: adjusted for age (in years), gender (men, women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other race/ethnicity).

Model 2: Model1 + education (less than high school, high school, college or higher), family income (family income to poverty ratio: 1.30, 1.31–3.50, > 3.50), cigarette smoking (never, past, current), physical activity (below, meet, exceed), alcohol intake (men: 0, 0.1–27.9 g/d, 28 g/d; women: 0, 0.1–13.9 g/d, 14 g/d), family history of diabetes (yes or no), total energy intake (quintiles), and HEI-2010 (quintiles).

Model 3: Model 2 + BMI (<25.0, 25.0–29.9, 30.0).

Table 5

Associations of plasma concentrations of *trans* fatty acids with glucose metabolism markers in individuals without diabetes

Variable	Biomarkers	Quintiles of plasma concentrations of <i>trans</i> fatty acids					P for trend
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Total <i>trans</i> fatty acid	Fasting glucose, mg/dL	0 [Ref]	1.6 (0.6) *	2.1 (0.5)	1.9 (0.7)	2.1 (0.7)	0.007
	Fasting insulin, pmol/L	0 [Ref]	15.4 (2.9)	16.9 (3.6)	18.4 (4.1)	24.1 (4.6)	<0.001
	HOMA2-IR	0 [Ref]	0.3 (0.05)	0.3 (0.06)	0.3 (0.07)	0.45 (0.08)	<0.0001
	HbA1c, %	0 [Ref]	-0.01 (0.02)	0.01 (0.02)	0.01 (0.03)	0.09 (0.02)	0.003
Elaidic acid	Fasting glucose, mg/dL	0 [Ref]	1.5 (0.7)	1.6 (0.5)	1.7 (0.7)	1.8 (0.7)	0.002
	Fasting insulin, pmol/L	0 [Ref]	9.2 (3.9)	21.1 (4.7)	15.4 (4.1)	24.3 (5.1)	<0.001
	HOMA2-IR	0 [Ref]	0.2 (0.07)	0.4 (0.08)	0.3 (0.07)	0.5 (0.09)	<0.0001
	HbA1c, %	0 [Ref]	0.001 (0.02)	-0.01 (0.02)	0.04 (0.03)	0.08 (0.03)	<0.001
Linolelaidic acid	Fasting glucose, mg/dL	0 [Ref]	1.1 (0.5)	1.1 (0.6)	1.4 (0.6)	0.5 (0.7)	0.86
	Fasting insulin, pmol/L	0 [Ref]	6.6 (4.7)	1.2 (4.0)	5.4 (3.6)	-2.3 (4.5)	0.65
	HOMA2-IR	0 [Ref]	0.1 (0.08)	0.03 (0.07)	0.11 (0.07)	-0.04 (0.08)	0.70
	HbA1c, %	0 [Ref]	-0.01 (0.01)	-0.03 (0.02)	-0.02 (0.02)	-0.01 (0.03)	0.99
Palmitelaidic acid	Fasting glucose, mg/dL	0 [Ref]	1.0 (0.7)	1.4 (0.6)	1.6 (0.7)	1.7 (0.8)	0.03
	Fasting insulin, pmol/L	0 [Ref]	10.8 (3.3)	18.2 (3.7)	13.3 (3.6)	16.6 (3.7)	0.0002
	HOMA2-IR	0 [Ref]	0.2 (0.06)	0.3 (0.06)	0.3 (0.07)	0.3 (0.07)	0.0002
	HbA1c, %	0 [Ref]	-0.01 (0.02)	-0.03 (0.02)	0.002 (0.03)	0.01 (0.03)	0.36
Vaccenic acid	Fasting glucose, mg/dL	0 [Ref]	1.2 (0.4)	1.6 (0.6)	1.6 (0.7)	1.9 (0.8)	0.03
	Fasting insulin, pmol/L	0 [Ref]	11.2 (3.7)	10.8 (3.0)	12.9 (3.5)	15.5 (5.0)	0.001
	HOMA2-IR	0 [Ref]	0.2 (0.06)	0.2 (0.05)	0.2 (0.06)	0.3 (0.09)	0.0007
	HbA1c, %	0 [Ref]	-0.003 (0.02)	-0.01 (0.02)	0.03 (0.03)	0.04 (0.03)	0.006

* β coefficient; standard errors in parentheses (all such values).

The number of participants was 3,296 for the analysis of fasting glucose, 3,277 for fasting insulin, 3,277 for HOMA2-IR, and 3,288 for HbA1c.

Adjusted for age (in years), gender (men, women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other race/ethnicity), survey cycle (NHANES1999–2000 or 2009–2010), education (less than high school, high school, college or higher), family income (family income to poverty ratio: 1.30, 1.31–3.50, >3.50, or missing), cigarette smoking (never, past, current), physical

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activity (below, meet, exceed), alcohol intake (men: 0, 0.1–27.9 g/d, 28 g/d; women: 0, 0.1–13.9 g/d, 14 g/d), family history of diabetes (yes or no), total energy intake (quintiles), and HEL-2010 (quintiles).