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Associations between omega-6 polyunsaturated fatty acids, hyperinsulinemia and incident diabetes by race/ethnicity: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background & Aims—Omega-6 polyunsaturated fatty acids (PUFAs) have been shown to relate to insulin resistance and type 2 diabetes (T2D), but influence of race/ethnicity has not been investigated. The aim of this study was to determine whether omega-6 PUFAs, and estimated desaturase enzyme activity, are associated with fasting glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and incident T2D, and whether associations differ by race/ethnicity.

Methods—This study was conducted in the Multi-Ethnic Study of Atherosclerosis (MESA) (N=6,282). Associations between baseline plasma phospholipid fatty acids (LA, Linoleic Acid; GLA, γ -linoleic acid; DGLA, Dihomo- γ -linolenic acid; AA, arachidonic acid; D5D, delta-5 desaturase; D6D, delta-6 desaturase), fasting glucose, insulin, and HOMA-IR [(fasting insulin – fasting glucose)/22.5] were evaluated using linear regression. Associations between omega-6 PUFAs (N=5,508 after excluding diabetics at baseline) and T2D incidence were assessed using Cox proportional hazards regression. Analyses were replicated/ stratified by race/ethnicity (White, Black, Chinese, Hispanic) and tests for interaction were assessed by inclusion of a cross-product term in models.

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DISCLOSURE

The authors report no conflicts of interests exist.

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Results—In fully adjusted models, insulin and HOMA-IR were positively associated with LA (insulin: 0.213 per SD, $p=0.01$; HOMA-IR: 0.252 per SD, $p<0.001$), GLA (insulin: 0.010 per SD, $p<0.001$; HOMA-IR: 0.006 per SD, $p<0.001$), DGLA (insulin: 0.279 per SD, $p<0.001$; HOMA-IR: 0.175 per SD, $p<0.001$) and D6D activity (insulin: 0.001 per SD, $p<0.001$; HOMA-IR: 0.006 per SD, $p<0.001$), and inversely associated with AA (insulin -0.272 per SD, $p<0.001$; HOMA-IR: -0.125 per SD, $p=0.03$) and D5D activity (insulin: -0.530 per SD, $p<0.001$; HOMA-IR: -0.322 per SD, $p<0.001$), while weak or no associations were observed with fasting glucose, and associations appeared to differ by race/ethnicity. After accounting for HOMA-IR at baseline, LA was inversely (HR: 0.87, $p=0.003$) and DGLA (HR: 1.17, $p<0.001$) and AA (HR: 1.15, $p=0.001$) were positively associated with T2D in the overall population, but associations were attenuated or no longer present when stratified by race/ethnicity (P -interaction >0.05).

Conclusions—Results confirm previous reports that omega-6 PUFAs are associated with hyperinsulinemia. Findings suggest omega-6 PUFAs are more likely markers of hyperinsulinemia rather than a protective/risk factor for T2D and indicate racial/ethnic differences in associations, but further research is needed to confirm findings..

Keywords

Omega-6; fatty acids; hyperinsulinemia; Type 2 Diabetes; race/ethnicity; HOMA-IR

Introduction

Hyperinsulinemia is linked to many chronic diseases, including type 2 diabetes (T2D) (1). Fatty acids are similarly shown to have implications in metabolic health and disease (2, 3) including mediating acute inflammatory response and its resolution (4–6). While omega-3 polyunsaturated fatty acid (PUFAs) have been shown to influence metabolic dysfunction (2, 3, 7), and are associated with lower risk of incident T2D (8–10), research on omega-6 PUFAs is limited. Studies of omega-6 PUFAs, which include linoleic acid (LA), γ -linolenic acid (GLA), dihomo- γ -linolenic acid (DGLA) and arachidonic acid (AA), and metabolic dysfunction have been inconclusive. The essential fatty acid, and most prominent omega-6 PUFA, LA is derived from diet, GLA and DGLA are primarily synthesized de-novo, and AA is a combination of both dietary intake and endogenous production. Early studies suggested LA and AA induced inflammation (11), whereas recent studies have shown LA to be associated with lower risks of metabolic dysfunction, including T2D (8, 12). Interestingly, GLA and DGLA may have paradoxical effects as they have been shown to mitigate conditions involving inflammation (13–15) while also being positively associated with inflammatory markers (16) and metabolic dysfunction (8–9, 12, 20–21). GLA, DGLA and AA levels are determined, in part, by elongase and desaturase enzymes. Delta-6 desaturase (D6D) converts LA to GLA, which is then elongated to DGLA and can then be converted to AA by delta-5 desaturase (D5D). These desaturases have been shown to be regulated by endocrine factors including insulin (13–15). Overall, it remains unclear whether omega-6 PUFAs, and associated metabolic enzymes, are associated with hyperinsulinemia or T2D risk.

Race/ethnicity may serve as a critical modifying variable of omega-6 PUFAs, hyperinsulinemia and T2D risk, however, these associations have not been studied across

races/ethnicities, in spite of key racial/ethnic differences in both the prevalence of insulin resistance and T2D and measured omega-6 PUFA levels. Prevalence of T2D is significantly higher in Black and Hispanic populations compared to Whites (22), and omega-6 PUFA profiles have been shown to vary by race/ethnicity in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (23). Therefore, the aim of the current study was to determine whether plasma phospholipid levels of omega-6 PUFAs LA, GLA, DGLA, and AA and estimated enzyme activity of D5D and D6D are related to metabolic dysfunction assessed by homeostasis model assessment of insulin resistance (HOMA-IR), fasting glucose and insulin levels, and incident T2D, and whether associations differ by race/ethnicity among White, Black, Hispanic and Chinese American participants in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.

Materials and Methods

Population

The primary aim and study design of MESA have been previously described (24), and detailed information is available online at <http://www.mesa-nhlbi.org>. Briefly, MESA is made up of 6,814 adult men and women aged 45 to 84 years without evidence of overt cardiovascular disease at the time of recruitment. The multi-ethnic sample of self-reported White, Black, Chinese, and Hispanic subjects was recruited from six communities across the U.S. (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St. Paul, MN). Each field site recruited from locally available sources, which included lists of residents, lists of dwellings, and telephone exchanges. In the last few months of the recruitment period, supplemental sources (lists of Medicare beneficiaries from the Centers for Medicare and Medicaid Services and referrals by participants) were used to ensure numbers of minorities and elderly subjects. Institutional Review Board approval was obtained at all MESA sites, and all participants gave informed consent.

Participants with missing diabetes data at baseline or during follow-up (N=5) and missing plasma phospholipid fatty acid (N=241) or other covariate data (N=286) were excluded resulting in a study sample of 6,282 participants for cross-sectional analyses. An additional 774 participants who were diabetic at baseline were excluded from the T2D incidence analysis (N=5,508).

Plasma and Serum Methods

Twelve-hour fasting blood were collected and stored in EDTA-anticoagulant tubes and serum tubes at -70°C using a standardized protocol (24). Serum insulin was measured by the Linco Human Insulin Specific RIA Kit (Linco Research, Inc., St. Charles, MO), and serum glucose was measured by rate reflectance spectrophotometry using thin-film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY) in accordance with the Centers for Disease Control and Prevention–standardized methods. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) calculated with the following equation: $\text{HOMA-IR} = [\text{fasting insulin (mIU/L)} - \text{fasting glucose (mmol/L)}]/22.5$.

EDTA plasma from the first examination was used for extraction of phospholipid fatty acid profiles using the previously described method by Cao et al. (25). Briefly, lipids were extracted with chloroform/methanol, separated using thin-layer chromatography, and the phospholipid band was derivatized to methyl esters. The final product was injected onto a capillary Varian CP7420 100-m column with a Hewlett Packard 5890 gas chromatograph with a flame ionization detector (GC-FID), interfaced with HP Chemstation software. Fatty acids are expressed as a percent of total phospholipid fatty acids. The following representative coefficients of variation were obtained for the relevant PUFAs (n=150): LA, 6.8%; GLA, 16.4%; DGLA, 9.2%; AA, 8.4%. The following equations were used to estimate desaturase activity levels: delta-5 desaturase (D5D): AA/DGLA; delta-6 desaturase (D6D): GLA/LA.

Demographic and Anthropometric Characteristics

Information regarding age, sex, self-reported race/ethnicity, education, alcohol consumption (never/rarely, former or current regular drinkers with usual consumption of 1 or 2 drinks/day for females and males, respectively) and medication and lifestyle factors were obtained by questionnaires and blood pressure, waist circumference (cm), height (m) and body weight (kg) were measured by trained study staff according to standard procedures (24). Body mass index (BMI) was tabulated from measured height and weight as body weight (kilograms) divided by height (meters) squared.

Incident Type 2 Diabetes

Type 2 diabetes (T2D) incidence through 2015 was ascertained at 5 follow-up exams and 12 follow-up contacts (through 2015) and was defined as being non-diabetic at baseline and by meeting at least one the following criteria: reported physician diagnosis, use of anti-diabetes medications, or fasting (12-h) glucose >126 mg/dL.

Statistical Methods

Descriptive statistics for participant demographics, lifestyle, and clinical characteristics were calculated, including, mean, SD, minimum, median and maximum for continuous variables, and frequencies for categorical variables by race/ethnicity. Population characteristics and biomarker concentrations by race/ethnicity and T2D status were evaluated using one-way ANOVA and Wald χ^2 tests. Associations between biomarkers were evaluated overall and by race/ethnicity using Spearman correlation. HOMA-IR, estimated desaturase enzyme activity and fasting insulin were log-transformed to normalize the distribution.

Cross-sectional associations between HOMA-IR, fasting glucose and insulin, with omega-6 PUFAs and estimated desaturase activity were evaluated using linear regression models with HOMA-IR, fasting glucose and insulin modeled as the predictor variables because of their hypothesized role in desaturase activity (9, 12–15). HOMA-IR, fasting glucose and insulin were modeled as quartiles and continuous variables (log-transformed, per unit increase). Quartile cut-points were the following: HOMA-IR = 1.282, 1.900, 2.967; insulin = 6.02, 8.27, 12.1; and fasting glucose = 83.0, 90.0, 99.0. Unadjusted and covariate-adjusted models were conducted including factors previously shown to be associated with omega-6 PUFAs and/or HOMA-IR, fasting glucose or insulin. The following covariates were included in the

final model: age, sex, education, systolic blood pressure, hypertension medication, BMI, smoking status (never, former, current), and alcohol consumption. Linear regression models were additionally conducted stratified by race/ethnicity and including a cross-product term in the model statement to assess interactions between race/ethnicity and HOMA-IR, fasting glucose or insulin.

Cox proportional hazards regression was used to tabulate hazard ratios (HR) for omega-6 PUFAs and estimated desaturase enzyme activity and incident T2D. Omega-6 PUFAs and estimated desaturase activity were evaluated categorically (quartiles) and continuously [per standard deviation (SD) increase]. Quartile cut-points were as follows: LA=17.97, 20.06, 22.29; GLA=0.079, 0.107, 0.139; DLGA=2.586, 3.103, 3.696; AA=9.87, 11.56, 13.36; D5D=2.947, 3.745, 4.732; D6D=0.00668, 0.00923, 0.0124. Models were conducted unadjusted and with adjustment for the same covariates used in the linear regression models. Models were additionally run including baseline fasting glucose and insulin levels or HOMA-IR to evaluate whether associations between omega-6 PUFAs or estimated desaturase activity and T2D remained after accounting for existing metabolic dysfunction at baseline. To examine the differential effects of omega-6 PUFAs across racial/ethnic groups, all analyses were replicated stratified by race/ethnicity and tests for interaction were performed by including a cross-products term in models.

A secondary analysis was conducted to preliminarily assess genotypes by race/ethnicity for *FADS2*, which was previously found to be associated with omega-6 PUFAs in MESA (26). Allele frequencies for *FADS2* were tabulated by race/ethnicity and unadjusted linear regression models were conducted to evaluate DGLA levels for each SNP by race/ethnicity. Statistical significance was defined as $P < 0.05$. Statistical analysis was conducted using SAS (version 9.4, SAS Institute Inc., Cary, NC).

Results

Baseline characteristics

There were 774 prevalent cases of T2D, and 860 individuals with impaired fasting glucose, among the 6,282 participants included in this study with a higher prevalence observed among Blacks and Hispanics. An additional 635 incident cases of diabetes were diagnosed among 5,508 participants free of diabetes at baseline through follow-up of which 31.2% were White, 28.8% were Black, 27.6% were Hispanic, and 12.4% were Chinese. Baseline demographic and biomarker concentrations stratified by race/ethnicity are shown in Table 1. White participants were more likely to be older, former smokers, to be current alcohol drinkers, have attained a higher level of education, have higher incomes, have normal fasting glucose, and lower incidence of developing T2D. Chinese participants were more likely to have impaired fasting glucose, a lower BMI and waist circumference, to not consume alcohol, and to have never smoked. Black participants were more likely to be female, had higher blood pressure and were more likely to have hypertension and to be taking hypertension medication. Hispanic participants had lower education levels and lower income.

Baseline fasting glucose, insulin, HOMA-IR, omega-6 PUFAs and estimated desaturase activity levels among non-cases and incident type 2 diabetics by race/ethnicity are presented in Table 2. AA levels and estimated D5D activity were highest among Blacks and LA levels were highest and DGLA levels were lowest among Chinese. Fasting glucose and HOMA-IR measurements were highest among participants with incident T2D relative to non-diabetics across all racial/ethnic groups. DGLA levels were lowest among non-cases and highest among incident cases for all racial/ethnic groups except Hispanics, where prevalent diabetics had the lowest levels. Omega-6 PUFAs were most strongly correlated with HOMA-IR, followed by insulin and fasting glucose, respectively (Supplementary Table 1). Across all racial/ethnic groups GLA, DGLA and D6D estimated activity were positively correlated and D5D estimated activity were negatively correlated with HOMA-IR. Conversely, LA was inversely associated with HOMA-IR among Whites and Blacks, but positively correlated among Chinese and Hispanics and AA was positively associated among Whites, inversely associated among Hispanics and not associated in Blacks and Chinese.

Omega-6 PUFAs, HOMA-IR, insulin, and fasting glucose

In fully adjusted models, HOMA-IR was positively associated with LA, GLA, DGLA and D6D activity, and inversely associated with AA and D5D activity (Table 3). Results were attenuated when stratified by race/ethnicity. Positive associations with HOMA-IR remained for LA in Hispanics and borderline among Chinese (continuous model only) (continuous HOMA-IR model P-interaction<0.001), GLA in Whites and Blacks (continuous HOMA-IR model P-interaction=0.01), DGLA in all race/ethnicities except Chinese (continuous HOMA-IR model P-interaction=0.002), and D6D in Whites and Hispanics (continuous HOMA-IR model P-interaction=0.09). HOMA-IR was strongly inversely associated with AA in Hispanics only (continuous HOMA-IR model P-interaction<0.001). D5D activity remained inversely associated among all racial/ethnic groups, but was not statistically significant among Chinese (HOMA-IR continuous model P-interaction=0.30).

Similar to HOMA-IR, insulin was positively associated with LA, GLA, DGLA and D6D and inversely associated with AA and D5D activity in multivariable-adjusted models (Table 4). When stratified by race/ethnicity, positive associations remained with LA among Hispanics (categorical and continuous models) and Chinese (categorical model only) (continuous insulin model P-interaction<0.001), GLA among all racial/ethnic groups except Hispanics (continuous insulin model P-interaction=0.01), and both DGLA (continuous insulin model P-interaction<0.001) and D6D (continuous insulin model P-interaction=0.03) among all racial/ethnic groups. Insulin was statically significantly inversely associated with AA among Hispanics only (continuous insulin model P-interaction<0.001) and among all races/ethnicities for D5D estimated activity (continuous insulin model P-interaction=0.10).

Fasting glucose was positively associated with LA when evaluated continuously only and associations remained significant only among Hispanics (continuous fasting glucose model P-interaction=0.02) (Table 5). Positive associations were also observed with AA, which were significant only among Whites (categorical and continuous models) and Blacks (continuous model only) (continuous fasting insulin model P-interaction=0.005), and with D5D when evaluated continuously only and remained statistically significant in Hispanics and Chinese

(continuous fasting glucose model P-interaction=0.54). Fasting glucose and DGLA were inversely associated and results were only statistically significant among Chinese and Hispanic participants (continuous fasting glucose model P-interaction=0.008). Fasting glucose and D6D estimated activity were modestly inversely associated, but associations were only borderline significant among Whites and Chinese in continuous models and non-significant in the overall population or among Blacks and Hispanics (continuous fasting insulin model P-interaction=0.55).

A full assessment of the role of genetics is beyond the scope of this current project due to sample size limitations; however, a preliminary evaluation of allele frequencies in the *FADS2* gene cluster demonstrates clear differences in allele frequencies by race/ethnicity in this population (Supplementary Table 2). In unadjusted linear regression models, β 's and 95% CI for DGLA levels per each additional coded allele (homozygous for non-coded allele $\rightarrow$ heterozygous homozygous $\rightarrow$ for coded allele) were similar across racial/ethnic groups, except among Chinese, which may be due to the smaller number of Chinese participants (Supplementary Table 3).

Omega-6 PUFAs and Incident Type 2 Diabetes after adjustment for hyperinsulinemia

Several omega-6 PUFAs were associated with T2D incidence in multivariable-adjusted models, including after adjustments for HOMA-IR or fasting glucose and insulin. Results for associations adjusted for HOMA-IR are presented on Table 6 models unadjusted for HOMA-IR, insulin or fasting glucose (Supplementary Table 4) and adjusted for fasting glucose and insulin (Supplementary Table 5). LA was inversely associated with T2D incidence in the overall population (per SD increase in LA HR=0.87, 95% CI: 0.80, 0.95) after multivariable adjustment including HOMA-IR. Inverse associations were also present when stratified by race/ethnicity, but were statistically significant among Whites only (per SD increase in LA HR=0.82, 95% CI: 0.69, 0.97). GLA was not associated in the overall population with T2D incidence, but was positively associated among Hispanics (per SD increase in GLA HR=1.19, 95% CI: 1.03, 1.37). DGLA was associated with higher risk of T2D in the overall model, but was statistically significant only when evaluated continuously (per SD increase in DGLA HR=1.17, 95% CI: 1.07, 1.27). In stratified models, the associations with DGLA remained only among Hispanics (per SD increase in DGLA HR=1.34, 95% CI: 1.14, 1.58). AA was also positively associated with T2D incidence in the overall population (per SD increase in AA HR=1.15, 95% CI: 1.06, 1.25), but associations only remained statistically significant for Whites in the categorical model (quartile 4 versus quartile 1 HR=1.60, 95% CI: 1.06, 2.40) and Blacks in the continuous model (per SD increase in AA HR=1.25, 95% CI: 1.08, 1.48). Estimated desaturase activity was not associated with T2D, except for D6D evaluated categorically in Hispanics (quartile 4 versus quartile 1 HR=2.07, 95% CI: 1.26, 3.42). A modest statistically significant interaction was observed in continuous models for D6D and race/ethnicity (P-interaction=0.04). All other tests for interaction between omega-6 PUFAs and race/ethnicity were not statistically significant.

Discussion

In this diverse population, hyperinsulinemia prevalence and T2D incidence differed by race/ethnicity, as did levels of omega-6 PUFAs, even after accounting for hyperinsulinemia or T2D status. Omega-6 PUFAs were associated with HOMA-IR and insulin levels, but were weakly or not associated with fasting glucose. These associations appeared to differ by race/ethnicity. LA was inversely, and DGLA and AA were positively, associated with T2D incidence in the overall population, but these associations generally were no longer present when stratified by race/ethnicity and tests for interaction were not significant.

Consistent with our results, insulin was previously reported to be positively associated with GLA, DGLA, and estimated D6D activity and inversely associated with estimated D5D activity in most (21, 29–30), but not all studies (3, 31). Data on associations between LA, AA and insulin resistance are inconclusive (20, 29–31). Our results agree with previously reported positive associations between LA and insulin resistance and inverse associations with AA when evaluated in the overall population but associations remained only in Hispanics when stratified by race/ethnicity. To our knowledge, no other study has examined differences by race/ethnicity. Our results suggest associations may differ by race/ethnicity for omega-6 PUFAs, but did not appear to differ for estimated desaturase activity. In support of possible racial/ethnic interactions, we observed differences in allele frequencies for genes involved in regulating omega-6 PUFA metabolism. Lack of associations with estimated desaturase activity could be related to the limitations of this approach in assessing actual enzyme activity. While it has been widely used in prior studies (3, 7–9, 12, 14, 28, 32), this approach is derived from animal studies (33–34), and the validity has not been well-evaluated in human populations (35).

Previous reports on the association between omega-6 PUFAs, desaturase enzymes, and incident T2D have been inconsistent (8–9, 12, 21, 27–28). Similar to our study, the European Prospective Investigation into Cancer and Nutrition cohort showed higher levels of GLA and DGLA were associated with greater risk of incident T2D whereas higher levels of LA were inversely associated (8) when models were not adjusted for baseline insulin or fasting glucose levels. In contrast with our results, they reported a null finding for AA. A meta-analysis of 20 prospective studies showed LA levels were inversely associated with incidence of T2D, and no association was observed with AA (36). While our results are consistent with previous studies (8,36), we hypothesized observed associations between GLA and DGLA with T2D incidence may merely be markers of hyperinsulinemia as most prior studies have not accounted for insulin levels at time of omega-6 PUFA measurements. Therefore, we examined associations with and without adjustment for HOMA-IR, insulin and fasting glucose levels at baseline. Results were attenuated after accounting for hyperinsulinemia, suggesting associations between omega-6 PUFAs and T2D incidence maybe due to the former being marker of metabolic changes in prediabetes, rather than direct influence on risk for T2D.

Insulin levels may be the primary driver of these associations as fasting glucose levels were not associated with omega-6 PUFAs. This is consistent with animal and *in vitro* study findings that insulin induces transcriptional activation of fatty acid desaturase genes, *FADS1*

and *FADS2*, which encode enzymes for D6D and D5D (15, 37–38). Specifically, insulin stimulates D6D resulting in greater conversion of LA to GLA and, subsequently, to DGLA. Concomitant with stimulating D6D, increased long-chain PUFAs suppress D5D activity resulting in a diminished conversion of DGLA to AA (13, 15). Insulin-regulated desaturase activity is supported by the present results whereby insulin levels were directly related to D6D ($p<0.001$) and inversely related to D5D ($p<0.001$), while fasting glucose was generally not associated with either. In an environment of peripheral insulin resistance where pancreatic beta cells are secreting greater amounts of insulin in response to higher blood glucose, DGLA synthesis appears to be stimulated while its metabolism to AA is reduced. Once pancreatic beta cells can no longer adequately produce insulin to counteract high glucose concentrations, metabolism of DGLA to AA appears to return to pre-hyperinsulinemia rates.

Racial differences in metabolic disease prevalence has been reported (39) with higher prevalence of insulin resistance in Blacks compared to Whites (40–41) and a two- to three-fold excess risk of developing non-insulin dependent T2D among Blacks and Hispanics compared with Whites (42–43). This is evident in the current study with racial/ethnic differences in T2D incidence and measured omega-6 PUFAs, insulin, and fasting glucose. We previously demonstrated subtle differences across MESA racial/ethnic groups with diet in four main food groups (whole grains, meat, seafood, and fruits and vegetables) (44). Dietary intake of LA was higher among Blacks and lowest among Chinese, however, dietary intake of AA was higher in Blacks but not different amongst the other race/ethnicities. Thus, differences in omega-6 PUFAs could be due to differences in *FADS1* and *FADS2* genotypes across race/ethnicities (45). Recent studies indicate the rate of conversion of LA to GLA to DGLA and, finally, to AA is partly due to large genetic variability in the *FADS* gene cluster (46–49). However, it remains unknown if observed genetic variability, and resulting differences in omega-6 PUFA levels, contributes to divergent disease risks by race/ethnicity.

Possible gene-insulin interactions on omega-6 PUFA levels may have relevance for racial/ethnic differences in T2D-related complications. While DGLA has been associated with inflammatory markers (19), anti-inflammatory and anti-proliferative effects have been reported (16–18). In mice with atopic dermatitis, an inflammatory skin condition, GLA prevented disease development (50). GLA supplementation in interventional studies correlates with reduced symptoms of inflammatory diseases such as asthma (16), atopic dermatitis (17), and rheumatoid arthritis (18). Therefore, one possible explanation is the increased DGLA synthesis in response to high insulin may be a compensatory mechanism which mitigates the harmful effects of hyperinsulinemia. In fact, we previously observed diabetic individuals with higher DGLA levels are less likely to develop retinopathy, an inflammatory complication of T2D (51).

This study has a several strengths. The multi-ethnic cohort allows observations to be more applicable to the US population. Our analysis by race/ethnicity provides greater detail into the differences and risks associated with omega-6 PUFAs and is the first to report on Blacks or Hispanics. The relatively large cohort size provided for a considerable number of incident T2D cases. The combination of cross-sectional and prospective data collection and corresponding analyses allowed an evaluation of whether presence of baseline

hyperinsulinemia accounted for associations between omega-6 PUFAs and T2D. Individual PUFAs were measured in plasma providing an objective measure of fatty acid levels and avoiding issues inherent in calculating PUFA intake through questionnaires and dietary recall. However, some limitations exist. Fatty acid data were only available at baseline, so our results do not reflect possible changes in fatty acids during follow-up. Additionally, HOMA-IR is widely used for estimating insulin resistance, but may inaccurately evaluate insulin resistance when pancreatic function is compromised (52). While genotypic associations with fatty acids and population frequencies support our findings of race-DGLA interaction with markers of insulin resistance, genetic factors for the observed racial/ethnic differences in DGLA and insulin resistance association cannot be determined from this analysis.

Conclusions

Our results suggest omega-6 PUFAs are associated with hyperinsulinemia, are more likely markers of hyperinsulinemia rather a true protective/risk factor for T2D, and associations may differ by race/ethnicity. The associations between hyperinsulinemia, omega-6 PUFAs, and racial/ethnic differences may have important implications for insulin resistance and T2D-related complications, and warrants further research. Future studies should be conducted, investigating whether differences by race/ethnicities are due, in part, to genetic variability in the *FADS* gene cluster and whether gene-hyperinsulinemia interactions explain racial/ethnic differences in risk for T2D-related complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

T2D	Type 2 diabetes
PUFAs	Polyunsaturated fatty acids
LA	Linoleic Acid
GLA	γ -linoleic acid
DGLA	Dihomo- γ -linolenic acid
AA	arachidonic acid
D5D	delta-5 desaturase

D6D	delta-6 desaturase
HOMA-IR	Homeostasis model assessment of insulin resistance
MESA	Multi-Ethnic Study of Atherosclerosis
GC-FID	Gas Chromatography-Flame Ionization Detection
BMI	Body mass index
HR	Hazard ratio
FADS	fatty acid desaturase

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Table 1. Baseline characteristics by race/ethnicity in the Multiethnic Study of Atherosclerosis Cohort (N=6,282).

	White N=2,444	Black N=1,647	Chinese N=784	Hispanic N=1,407	p-value [†]
Age, median (IQR)	63.0 (54.0, 71.0)	61.0 (53.0, 69.0)	62.0 (53.0, 70.5)	61.0 (52.0, 69.0)	<0.001
Sex, n (% female)	1268 (51.9)	922 (56.0)	403 (51.4)	721 (51.2)	0.02
Education, n (%)					<0.001
<High school	119 (4.9)	184 (11.2)	192 (24.5)	626 (44.9)	
High school/GED	403 (16.5)	307 (18.6)	128 (16.3)	286 (20.3)	
Some college/associate's degree	690 (28.2)	580 (35.2)	155 (19.8)	356 (25.3)	
Bachelor's degree	552 (22.6)	294 (17.9)	179 (22.8)	74 (5.3)	
Graduate/professional school	680 (27.8)	282 (17.1)	130 (16.6)	65 (4.6)	
Income, n (%)					<0.001
<\$25,000	388 (15.9)	499 (30.3)	385 (49.1)	701 (49.8)	
\$25,000 - <\$40,000	387 (15.8)	354 (21.5)	124 (15.8)	338 (24.0)	
\$40,000 - <\$75,000	763 (31.2)	505 (30.7)	141 (18.0)	268 (19.1)	
\$75,000	906 (37.1)	289 (17.6)	134 (17.1)	100 (7.1)	
Smoking history, n (%)					<0.001
Never	1069 (43.7)	754 (45.8)	593 (75.6)	755 (53.7)	
Former	1082 (44.3)	602 (36.6)	146 (18.6)	462 (32.8)	
Current	293 (12.0)	291 (17.7)	45 (5.7)	190 (13.5)	
Alcohol intake, n (%)					<0.001
Never	225 (9.2)	278 (16.9)	422 (53.8)	361 (25.7)	
Former	449 (18.4)	534 (32.4)	115 (14.7)	376 (26.7)	
Current	1770 (72.4)	835 (50.7)	247 (31.5)	670 (47.6)	
Hypertension, n (%)	942 (38.5)	953 (57.9)	291 (37.1)	576 (40.9)	<0.001
Hypertension Medication, n (%)	806 (33.0)	801 (48.6)	224 (28.6)	454 (32.3)	<0.001
BMI (m/kg ²), median (IQR)	27.1 (24.2, 30.4)	29.4 (26.3, 33.6)	23.8 (21.7, 26.0)	28.7 (26.0, 31.9)	<0.001
WC (cm), median (IQR)	97.3 (88.0, 106.9)	99.8 (91.5, 110.0)	86.9 (80.5, 93.5)	99.2 (91.8, 107.8)	<0.001
Baseline diabetes status, n (%)					<0.001
Normal Fasting Glucose	2024 (82.8)	1132 (68.7)	545 (69.5)	947 (67.3)	
Impaired Fasting Glucose	278 (11.4)	231 (14.0)	133 (17.0)	218 (15.5)	

	White N=2,444	Black N=1,647	Chinese N=784	Hispanic N=1,407	^I p-value
Prevalent diabetes	142 (5.8)	284 (17.2)	106 (13.5)	242 (17.2)	
Incident diabetes, n (%)	198 (8.6)	183 (13.4)	79 (11.7)	175 (15.0)	

Abbreviations: BMI: Body Mass Index; LA: Linoleic Acid; GLA: Gamma-Linolenic Acid; DGLA: Dihomo-Gamma-Linolenic Acid; AA: Arachidonic Acid; D5D: Estimated delta-5 desaturase activity (AA/DGLA); D6D: Estimated delta-6 desaturase activity (GLA/LA), WC: waist circumference.

^I One-way ANOVA-continuous variables; Wald χ^2 tests-categorical variables.

Table 2.

Baseline fasting glucose, insulin, HOMA-IR and omega-6 PUFAs levels among non-cases and incident diabetics by race/ethnicity

	Whites	Blacks	Chinese	Hispanics	P-Value ^I
Non-Cases (N=4,873)					
N (%)	2104 (43.2)	1180 (24.2)	599 (12.3)	990 (20.3)	---
Fasting glucose, median (IQR)	86.0 (80.0, 92.0)	88.0 (82.0, 94.0)	89.0 (84.0, 95.0)	88.0 (82.0, 95.0)	<0.001
Insulin, median (IQR)	7.02 (5.40, 10.14)	8.15 (5.77, 11.9)	7.52 (5.90, 10.3)	8.40 (6.24, 12.0)	<0.001
HOMA-IR, median (IQR)	1.51 (1.11, 2.22)	1.78 (1.22, 2.68)	1.66 (1.28, 2.36)	1.83 (1.29, 2.69)	<0.001
LA (% total), median (IQR)	19.8 (17.9, 21.8)	19.0 (17.2, 20.9)	23.1 (20.6, 25.4)	20.9 (18.8, 23.1)	<0.001
GLA (% total), median (IQR)	0.11 (0.09, 0.15)	0.10 (0.08, 0.13)	0.08 (0.05, 0.12)	0.11 (0.09, 0.14)	<0.001
DGLA (% total), median (IQR)	3.10 (2.60, 3.69)	2.84 (2.43, 3.31)	2.71 (2.18, 3.23)	3.53 (2.99, 4.08)	<0.001
AA (% total), median (IQR)	11.2 (9.69, 12.7)	13.0 (11.3, 14.6)	10.3 (8.89, 11.7)	11.0 (9.37, 12.7)	<0.001
D5D, median (IQR)	3.59 (2.89, 4.46)	4.58 (3.76, 5.50)	3.80 (3.10, 4.87)	3.13 (2.44, 3.97)	<0.001
D6D, median (IQR)	0.010 (0.008, 0.014)	0.008 (0.006, 0.010)	0.008 (0.005, 0.011)	0.010 (0.007, 0.013)	<0.001
Incident Cases (N=635)<					
N (%)	198 (31.2)	183 (28.8)	79 (12.4)	183 (27.6)	---
Fasting glucose, median (IQR)	99.5 (92.0, 111.0)	100.0 (91.0, 108.0)	100.0 (92.0, 112.0)	101.0 (91.0, 112.0)	0.72
Insulin, median (IQR)	11.5 (8.15, 16.63)	11.0 (8.22, 15.0)	10.6 (7.02, 15.5)	12.7 (9.77, 17.9)	0.03
HOMA-IR, median (IQR)	2.83 (1.97, 4.19)	2.78 (1.96, 3.77)	2.76 (1.77, 3.98)	3.29 (2.34, 4.48)	0.03
LA (% total), median (IQR)	19.0 (17.2, 21.1)	18.6 (16.6, 20.4)	22.7 (20.5, 24.5)	20.7 (18.9, 22.6)	<0.001
GLA (% total), median (IQR)	0.12 (0.09, 0.16)	0.10 (0.08, 0.13)	0.09 (0.06, 0.14)	0.12 (0.09, 0.16)	0.003
DGLA (% total), median (IQR)	3.47 (2.91, 4.10)	3.07 (2.58, 3.46)	3.02 (2.53, 3.52)	3.89 (3.36, 4.54)	<0.001
AA (% total), median (IQR)	11.7 (9.89, 13.4)	13.5 (11.8, 15.4)	10.7 (8.93, 12.1)	11.1 (9.62, 13.0)	<0.001
D5D, median (IQR)	3.27 (2.66, 4.24)	4.47 (3.85, 5.19)	3.58 (3.06, 4.31)	2.92 (2.19, 3.54)	<0.001
D6D, median (IQR)	0.011 (0.00, 0.014)	0.008 (0.006, 0.011)	0.009 (0.006, 0.013)	0.011 (0.008, 0.014)	<0.001

Abbreviations: LA: Linoleic Acid; GLA: Gamma-Linolenic Acid; DGLA: Dihomo-Gamma-Linolenic Acid; AA: Arachidonic Acid; D5D: Estimated delta-5 desaturase activity (AA/DGLA); D6D: Estimated delta-6 desaturase activity (GLA/LA); PUFA: polyunsaturated fatty acid.

^IOne-way ANOVA.

Cross-sectional levels of individual plasma omega-6 fatty-acids by insulin resistance estimated by HOMA-IR overall and stratified by race/ethnicity.

Table 3.

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	
LA (18:2n6)						
HOMA-IR						0.001
Quartile 1	20.7 (20.0, 21.5)	19.1 (18.0, 20.3)	18.3 (16.5, 20.1)	23.1 (22.4, 23.8)	21.8 (20.6, 23.1)	
Quartile 2	20.8 (20.0, 21.5)	19.2 (18.1, 20.4)	18.0 (16.2, 19.8)	23.0 (22.5, 23.6)	22.1 (20.9, 23.4)	
Quartile 3	20.9 (20.1, 21.6)	19.2 (18.1, 20.4)	18.0 (16.2, 19.8)	23.3 (22.7, 23.8)	22.1 (20.9, 23.3)	
Quartile 4	21.1 (20.3, 21.8)	19.2 (18.1, 20.4)	18.0 (16.2, 19.8)	23.6 (22.9, 24.2)	22.8 (21.6, 24.0)	
P-Value ⁴	0.005	0.62	0.29	0.32	< 0.001	
Per 1 unit increase	0.252 (0.106, 0.398)	0.109 (-0.151, 0.369)	0.015 (-0.219, 0.248)	0.598 (0.038, 1.168)	0.510 (0.220, 0.799)	< 0.001
P-Value	< 0.001	0.41	0.90	0.04	< 0.001	
GLA (18:3n6)						
HOMA-IR						0.34
Quartile 1	0.101 (0.078, 0.114)	0.112 (0.091, 0.133)	0.142 (0.110, 0.174)	0.091 (0.080, 0.101)	0.096 (0.075, 0.116)	
Quartile 2	0.110 (0.096, 0.123)	0.121 (0.100, 0.142)	0.150 (0.118, 0.182)	0.096 (0.087, 0.104)	0.109 (0.088, 0.130)	
Quartile 3	0.110 (0.097, 0.124)	0.124 (0.103, 0.145)	0.154 (0.122, 0.186)	0.092 (0.084, 0.101)	0.106 (0.086, 0.127)	
Quartile 4	0.113 (0.100, 0.126)	0.128 (0.107, 0.149)	0.157 (0.125, 0.188)	0.105 (0.094, 0.115)	0.103 (0.083, 0.123)	
P-Value ⁴	< 0.001	< 0.001	< 0.001	0.06	0.12	
Per 1 unit increase	0.006 (0.004, 0.009)	0.009 (0.005, 0.014)	0.009 (0.004, 0.013)	0.004 (-0.004, 0.013)	0.001 (-0.004, 0.006)	0.002
P-Value	< 0.001	< 0.001	< 0.001	0.33	0.65	
DGLA (20:3n6)						
HOMA-IR						0.36
Quartile 1	3.06 (2.88, 3.25)	3.01 (2.72, 3.31)	3.19 (2.77, 3.60)	2.69 (2.54, 2.83)	3.52 (3.19, 3.84)	
Quartile 2	3.18 (3.00, 3.37)	3.14 (2.84, 3.44)	3.37 (2.96, 3.78)	2.73 (2.62, 2.84)	3.65 (3.33, 3.97)	
Quartile 3	3.28 (3.09, 3.46)	3.29 (2.99, 3.59)	3.46 (3.05, 3.87)	2.70 (2.58, 2.82)	3.77 (3.45, 4.08)	

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LMeans(β (95% CI) ^{1,2}	LMeans(β (95% CI) ^{1,2}	LMeans(β (95% CI) ^{1,2}	LMeans(β (95% CI) ^{1,2}	LMeans(β (95% CI) ^{1,2}	
Quartile 4	3.38 (3.20, 3.56)	3.41 (3.11, 3.72)	3.56 (3.15, 3.97)	2.86 (2.72, 3.00)	3.85 (3.54, 4.17)	
P-Value ⁴	<0.001	<0.001	<0.001	0.09	<0.001	
Per 1 unit increase	0.175 (0.139, 0.211)	0.255 (0.187, 0.323)	0.155 (0.101, 0.208)	0.095 (-0.026, 0.215)	0.135 (0.059, 0.211)	0.002
P-Value	<0.001	<0.001	<0.001	0.13	<0.001	
AA (20-4n6)						
HOMA-IR						0.007
Quartile 1	11.7 (11.1, 12.3)	12.2 (11.4, 13.1)	14.0 (12.5, 15.6)	10.3 (9.87, 10.7)	10.8 (9.80, 11.8)	
Quartile 2	11.9 (11.3, 12.5)	12.4 (11.6, 13.3)	14.2 (12.6, 15.7)	10.6 (10.3, 11.0)	10.7 (9.76, 11.7)	
Quartile 3	11.8 (11.2, 12.3)	12.2 (11.3, 13.1)	14.2 (12.6, 15.7)	10.5 (10.1, 10.8)	10.6 (9.60, 11.5)	
Quartile 4	11.6 (11.1, 12.2)	12.3 (11.5, 13.2)	14.2 (12.6, 15.7)	10.5 (10.1, 10.9)	10.0 (9.07, 11.0)	
P-Value ⁴	0.38	0.48	0.41	0.50	<0.001	
Per 1 unit increase	-0.125 (-0.238, -0.012)	0.030 (-0.171, 0.231)	0.073 (-0.128, 0.273)	-0.173 (-0.515, 0.170)	-0.497 (-0.728, -0.266)	<0.001
P-Value ⁴	0.03	0.77	0.48	0.32	<0.001	
D5D						
HOMA-IR						0.06
Quartile 1	4.20 (3.56, 4.85)	4.27 (3.69, 4.85)	5.20 (2.28, 8.13)	4.16 (3.90, 4.42)	3.26 (2.79, 3.73)	
Quartile 2	3.98 (3.33, 4.62)	4.15 (3.57, 4.74)	4.42 (1.50, 7.34)	4.26 (4.06, 4.46)	3.13 (2.67, 3.60)	
Quartile 3	3.83 (3.18, 4.47)	3.96 (3.38, 4.55)	4.25 (1.34, 7.17)	4.25 (4.04, 4.46)	2.94 (2.48, 3.40)	
Quartile 4	3.66 (3.02, 4.31)	3.78 (3.19, 4.38)	4.19 (1.29, 7.09)	4.04 (3.78, 4.29)	2.72 (2.26, 3.18)	
P-Value ⁴	<0.001	<0.001	0.005	0.50	<0.001	
Per 1 unit increase	-0.322 (-0.447, -0.198)	-0.331 (-0.465, -0.196)	-0.403 (-0.780, -0.026)	-0.175 (-0.391, 0.040)	-0.279 (-0.389, -0.168)	0.30
P-Value ⁴	<0.001	<0.001	0.04	0.11	<0.001	
D6D						
HOMA-IR						0.14

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	
Quartile 1	0.0087 (0.0074, 0.0101)	0.0095 (0.0074, 0.0116)	0.0104 (0.0065, 0.0142)	0.0090 (0.0080, 0.0100)	0.0090 (0.0069, 0.0112)	
Quartile 2	0.0093 (0.0079, 0.0107)	0.0102 (0.0081, 0.0123)	0.0104 (0.0065, 0.0143)	0.0091 (0.0084, 0.0100)	0.0102 (0.0081, 0.0124)	
Quartile 3	0.0095 (0.0081, 0.0109)	0.0106 (0.0084, 0.0127)	0.0109 (0.0070, 0.0147)	0.0090 (0.0082, 0.0097)	0.0102 (0.0081, 0.0123)	
Quartile 4	0.0098 (0.0084, 0.0112)	0.0109 (0.0087, 0.0130)	0.0110 (0.0072, 0.0148)	0.0102 (0.0093, 0.0112)	0.0105 (0.0084, 0.0126)	
P-Value ⁴	<0.001	<0.001	0.18	0.08	0.004	
Per 1 unit increase	0.0006 (0.0003, 0.0009)	0.0008 (0.0003, 0.0012)	0.0004 (-0.0001, 0.0009)	0.0006 (-0.0002, 0.0014)	0.0006 (0.0001, 0.0011)	0.09
P-Value ⁴	<0.001	0.002	0.08	0.15	0.002	

Abbreviations: LA: Linoleic Acid; GLA: Gamma-Linolenic Acid; DGLA: Dihomo-Gamma-Linolenic Acid; AA: Arachidonic Acid; D5D: Estimated delta-5 desaturase activity (AA/DGLA); D6D: Estimated delta-6 desaturase activity (GLA/LA); int: interaction; PUFA: polyunsaturated fatty acid.

¹ Linear regression with HOMA_IR modeled as the predictor adjusted for age, race/ethnicity, gender, waist circumference, education level, hypertension medication use, cigarette smoking, alcohol intake

² LSmean N6-PUFAs for categorical evaluation of HOMA-IR, β per 1 unit change in HOMA-IR evaluated continuously.

³ Test for interaction assessed by inclusion of cross-product term in multivariable adjusted model.

⁴ Quartile 4 versus quartile 1.

⁵ Quartile cut-points for HOMA-IR: 1.282, 1.900, 2.967.

Table 4.

Cross-sectional levels of individual plasma omega-6 fatty-acids by insulin levels overall and stratified by race/ethnicity.

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	
LA (18:2n6)						
Insulin						0.005
Quartile 1	20.6 (19.9, 21.4)	19.2 (18.0, 20.3)	18.2 (16.4, 20.0)	22.7 (22.1, 23.3)	21.9 (20.6, 23.1)	
Quartile 2	20.9 (20.1, 21.6)	19.2 (18.1, 20.4)	18.1 (16.3, 19.9)	23.3 (22.8, 23.8)	22.3 (21.1, 23.5)	
Quartile 3	20.9 (20.2, 21.7)	19.3 (18.2, 20.4)	18.0 (16.2, 19.8)	23.3 (22.7, 23.8)	22.3 (21.1, 23.5)	
Quartile 4	21.1 (20.3, 21.8)	19.2 (18.1, 20.4)	18.0 (16.2, 19.8)	23.7 (23.0, 24.4)	22.6 (21.4, 23.8)	
P-Value ⁴	0.001	0.74	0.50	0.04	0.007	
Per 1 unit increase	0.213 (0.043, 0.384)	0.045 (-0.255, 0.345)	0.022 (-0.249, 0.293)	0.620 (-0.027, 1.27)	0.406 (0.062, 0.750)	<0.001
P-Value	0.01	0.77	0.87	0.06	0.02	
GLA (18:3n6)						
Insulin						0.40
Quartile 1	0.101 (0.088, 0.114)	0.111 (0.090, 0.132)	0.143 (0.111, 0.175)	0.087 (0.077, 0.097)	0.097 (0.076, 0.118)	
Quartile 2	0.109 (0.096, 0.122)	0.121 (0.100, 0.142)	0.149 (0.117, 0.181)	0.097 (0.088, 0.105)	0.106 (0.085, 0.127)	
Quartile 3	0.110 (0.097, 0.123)	0.124 (0.103, 0.145)	0.152 (0.120, 0.184)	0.095 (0.086, 0.104)	0.103 (0.083, 0.124)	
Quartile 4	0.114 (0.101, 0.127)	0.128 (0.107, 0.149)	0.158 (0.126, 0.189)	0.107 (0.096, 0.118)	0.106 (0.085, 0.126)	
P-Value ⁴	<0.001	<0.001	<0.001	0.009	0.05	
Per 1 unit increase	0.010 (0.007, 0.013)	0.013 (0.008, 0.019)	0.011 (0.006, 0.015)	0.011 (0.001, 0.021)	0.004 (-0.002, 0.009)	0.01
P-Value	<0.001	<0.001	<0.001	0.04	0.23	
DGLA (20:3n6)						
Insulin						0.47
Quartile 1	3.03 (2.85, 3.22)	2.98 (2.68, 3.27)	3.16 (2.75, 3.57)	2.60 (2.46, 2.73)	3.45 (3.13, 3.77)	
Quartile 2	3.20 (3.01, 3.38)	3.17 (2.87, 3.47)	3.36 (2.95, 3.77)	2.75 (2.64, 2.86)	3.64 (3.32, 3.96)	
Quartile 3	3.26 (3.08, 3.44)	3.29 (3.00, 3.59)	3.40 (3.00, 3.81)	2.70 (2.58, 2.82)	3.74 (3.43, 4.05)	

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LMeans(β (95% CI) ^{1,2}	LMeans(β (95% CI) ^{1,2}	LMeans(β (95% CI) ^{1,2}	LMeans(β (95% CI) ^{1,2}	LMeans(β (95% CI) ^{1,2}	
Quartile 4	3.03 (2.85, 3.22)	3.43 (3.13, 3.73)	3.60 (3.20, 4.01)	2.96 (2.82, 3.11)	3.94 (3.62, 4.25)	
P-Value ⁴	<0.001	<0.001	<0.001	<0.001	<0.001	
Per 1 unit increase	0.279 (0.237, 0.321)	0.337 (0.259, 0.416)	0.239 (0.177, 0.301)	0.235 (0.096, 0.374)	0.271 (0.181, 0.361)	0.02
P-Value	<0.001	<0.001	<0.001	<0.001	<0.001	
AA (20-4n6)						
Insulin						0.001
Quartile 1	11.9 (11.3, 12.5)	12.3 (11.4, 13.2)	14.2 (12.6, 15.8)	10.6 (10.2, 11.0)	11.0 (10.0, 12.0)	
Quartile 2	11.9 (11.3, 12.5)	12.5 (11.6, 13.3)	14.3 (12.8, 15.9)	10.5 (10.2, 10.8)	10.7 (9.4, 11.7)	
Quartile 3	11.7 (10.9, 12.1)	12.2 (11.3, 13.1)	14.1 (12.6, 15.7)	10.7 (10.3, 11.0)	10.5 (9.5, 11.4)	
Quartile 4	11.5 (10.9, 12.1)	12.2 (11.3, 13.1)	14.1 (12.5, 15.6)	10.1 (9.6, 10.5)	9.9 (9.0, 10.9)	
P-Value ⁴	<0.001	0.56	0.48	0.06	<0.001	
Per 1 unit increase	-0.272 (-0.404, -140)	-0.085 (-0.317, 0.147)	-0.099 (-0.331, 0.134)	-0.379 (-0.774, 0.015)	-0.669 (-0.943, -0.396)	<0.001
P-Value ⁴	<0.001	0.47	0.41	0.06	<0.001	
D5D						
Insulin						0.08
Quartile 1	4.31 (3.67, 4.96)	4.33 (3.76, 4.91)	5.32 (2.40, 8.24)	4.55 (4.31, 4.79)	3.43 (2.97, 3.89)	
Quartile 2	3.96 (3.31, 4.60)	4.13 (3.54, 4.71)	4.54 (1.62, 7.45)	4.13 (3.94, 4.33)	3.14 (2.68, 3.60)	
Quartile 3	3.83 (3.19, 4.47)	3.94 (3.36, 4.53)	4.36 (1.46, 7.27)	4.27 (4.05, 4.49)	2.93 (2.48, 3.38)	
Quartile 4	3.53 (2.89, 4.17)	3.72 (3.13, 4.31)	4.05 (1.16, 6.95)	3.75 (3.49, 4.01)	2.61 (2.15, 3.06)	
P-Value ⁴	<0.001	<0.001	<0.001	<0.001	<0.001	
Per 1 unit increase	-0.530 (-0.675, -0.385)	-0.446 (-0.601, -0.291)	-0.659 (-1.10, -0.22)	-0.540 (-0.876, -0.294)	-0.486 (-0.616, -0.356)	0.10
P-Value ⁴	<0.001	<0.001	0.003	<0.001	<0.001	
D6D						
Insulin						0.10

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	LSmeans/ β (95% CI) ^{1,2}	
Quartile 1	0.0087 (0.0073, 0.0100)	0.0094 (0.0073, 0.0115)	0.0103 (0.0064, 0.0142)	0.0084 (0.0075, 0.0093)	0.0090 (0.0068, 0.0111)	
Quartile 2	0.0091 (0.0078, 0.0105)	0.0100 (0.0079, 0.0122)	0.0103 (0.0064, 0.0141)	0.0093 (0.0086, 0.0100)	0.0099 (0.0078, 0.0120)	
Quartile 3	0.0094 (0.0081, 0.0108)	0.0106 (0.0085, 0.0127)	0.0107 (0.0068, 0.0145)	0.0090 (0.0081, 0.0098)	0.0101 (0.0080, 0.0122)	
Quartile 4	0.0100 (0.0086, 0.0114)	0.0110 (0.0088, 0.0131)	0.0112 (0.0074, 0.0150)	0.0107 (0.0097, 0.0117)	0.0107 (0.0087, 0.0128)	
P-Value ⁴	<0.001	<0.001	0.06	<0.001	<0.001	
Per 1 unit increase	0.0010 (0.0007, 0.0013)	0.0012 (0.0007, 0.0018)	0.0007 (0.0001, 0.0013)	0.0014 (0.0004, 0.0023)	0.0009 (0.0003, 0.0015)	0.03
P-Value ⁴	<0.001	<0.001	0.02	0.004	0.003	

Abbreviations: LA: Linoleic Acid; GLA: Gamma-Linolenic Acid; DGLA: Dihomo-Gamma-Linolenic Acid; AA: Arachidonic Acid; D5D: Estimated delta-5 desaturase activity (AA/DGLA); D6D: Estimated delta-6 desaturase activity (GLA/LA); int: interaction; PUFA: polyunsaturated fatty acid.

¹Linear regression with insulin modeled as the predictor adjusted for age, race/ethnicity, gender, waist circumference, education level, hypertension medication use, cigarette smoking, alcohol intake

²LSmean N6-PUFAs for categorical evaluation of insulin, β per 1 unit change in insulin evaluated continuously.

³Test for interaction assessed by inclusion of cross-product term in multivariable adjusted model.

⁴Quartile 4 versus quartile 1.

⁵Quartile cut-points for insulin: 6.02, 8.27, 12.1

Table 5.

Cross-sectional levels of individual plasma omega-6 fatty-acids by fasting glucose levels overall and stratified by race/ethnicity.

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LSmeans/p (95% CI) ^{1,2}	LSmeans/p (95% CI) ^{1,2}	LSmeans/p (95% CI) ^{1,2}	LSmeans/p (95% CI) ^{1,2}	LSmeans/p (95% CI) ^{1,2}	
LA (18:2n6) (% FA)						
Fasting glucose						0.06
Quartile 1	21.0 (20.2, 21.7)	19.3 (18.1, 20.4)	18.2 (16.4, 20.0)	23.7 (23.0, 24.5)	22.0 (20.8, 23.3)	
Quartile 2	20.8 (20.0, 21.5)	19.1 (17.9, 20.2)	18.1 (16.3, 19.9)	23.0 (22.5, 23.6)	22.2 (21.0, 23.5)	
Quartile 3	20.9 (20.1, 21.6)	19.4 (18.3, 20.5)	18.0 (16.3, 19.8)	23.2 (22.6, 23.7)	22.2 (21.0, 23.4)	
Quartile 4	20.9 (20.2, 21.7)	19.3 (18.2, 20.5)	17.9 (16.1, 19.7)	23.3 (22.7, 23.8)	22.5 (21.0, 23.4)	
P-Value ⁴	0.67	0.66	0.22	0.26	0.07	
Per 1 unit increase	0.59 (0.23, 0.96)	0.66 (−0.11, 1.44)	0.02 (−0.56, 0.60)	0.67 (−0.57, 1.92)	1.09 (0.44, 1.73)	0.02
P-Value	0.001	0.09	0.94	0.29	< 0.001	
GLA (18:3n6) (% FA)						
Fasting glucose						0.38
Quartile 1	0.105 (0.092, 0.129)	0.120 (0.099, 0.141)	0.148 (0.116, 0.180)	0.090 (0.078, 0.102)	0.097 (0.076, 0.118)	
Quartile 2	0.108 (0.095, 0.121)	0.116 (0.095, 0.137)	0.152 (0.120, 0.185)	0.096 (0.088, 0.105)	0.107 (0.086, 0.127)	
Quartile 3	0.111 (0.099, 0.125)	0.122 (0.101, 0.143)	0.154 (0.122, 0.186)	0.102 (0.093, 0.111)	0.105 (0.084, 0.126)	
Quartile 4	0.107 (0.094, 0.120)	0.117 (0.096, 0.139)	0.151 (0.120, 0.184)	0.093 (0.084, 0.101)	0.100 (0.080, 0.121)	
P-Value ⁴	0.47	0.50	0.33	0.69	0.40	
Per 1 unit increase	−0.004 (−0.010, 0.003)	−0.005 (−0.020, 0.009)	0.007 (−0.003, 0.017)	−0.019 (−0.039, 0.001)	−0.007 (−0.018, 0.004)	0.70
P-Value	0.24	0.47	0.19	0.06	0.23	
DGLA (20:3n6) (% FA)						
Fasting glucose						0.10
Quartile 1	3.17 (2.99, 3.36)	3.14 (2.84, 3.44)	3.37 (2.95, 3.79)	2.73 (2.56, 2.89)	3.70 (3.38, 4.03)	
Quartile 2	3.24 (3.05, 3.42)	3.16 (2.86, 3.46)	3.48 (3.06, 3.90)	2.80 (2.68, 2.92)	3.70 (3.38, 4.02)	
Quartile 3	3.24 (3.06, 3.43)	3.10 (2.80, 3.40)	3.48 (3.06, 3.89)	2.76 (2.64, 2.88)	3.74 (3.42, 4.06)	

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LMeans/p (95% CI) ^{1,2}	LMeans/p (95% CI) ^{1,2}	LMeans/p (95% CI) ^{1,2}	LMeans/p (95% CI) ^{1,2}	LMeans/p (95% CI) ^{1,2}	
Quartile 4	3.23 (3.05, 3.42)	2.31 (2.90, 3.51)	3.36 (2.95, 3.78)	2.69 (2.57, 2.80)	3.76 (3.44, 4.08)	
P-Value ⁴	0.05	0.24	0.87	0.69	0.86	
Per 1 unit increase	-0.188 (-0.279, -0.097)	0.014 (-0.193, 0.220)	-0.132 (-0.266, 0.002)	-0.413 (-0.681, -0.144)	-0.280 (-0.450, -0.110)	0.008
P-Value	<0.001	0.90	0.05	0.003	0.001	
AA (20:4n6) (% FA)						
Fasting glucose						0.05
Quartile 1	11.5 (10.9, 12.1)	12.1 (11.2, 12.9)	13.8 (12.2, 15.3)	10.1 (9.6, 10.6)	10.5 (9.5, 11.5)	
Quartile 2	11.8 (11.2, 12.3)	12.4 (11.5, 13.2)	14.2 (12.7, 15.8)	10.5 (10.1, 10.8)	10.4 (9.4, 11.4)	
Quartile 3	11.8 (11.2, 12.4)	12.4 (11.5, 13.3)	14.1 (12.6, 15.7)	10.5 (10.2, 10.9)	10.6 (9.6, 11.6)	
Quartile 4	11.8 (11.3, 12.4)	12.4 (11.5, 13.3)	14.6 (13.0, 16.1)	10.6 (10.2, 10.9)	10.3 (9.4, 11.3)	
P-Value ⁴	<0.001	0.02	0.06	0.09	0.37	
Per 1 unit increase	0.441 (0.160, 0.723)	0.827 (0.228, 1.43)	0.814 (0.320, 1.31)	0.571 (-0.192, 1.33)	-0.103 (-0.620, 0.414)	0.005
P-Value	0.002	0.007	0.001	0.14	0.70	
D5D (ratio)						
Fasting glucose						0.31
Quartile 1	4.02 (3.37, 4.67)	4.11 (3.52, 4.70)	4.79 (1.86, 7.71)	4.03 (3.74, 4.33)	2.98 (2.50, 3.45)	
Quartile 2	3.87 (3.23, 4.51)	4.11 (3.53, 4.69)	4.28 (1.36, 7.20)	4.04 (3.83, 4.25)	2.98 (2.41, 3.44)	
Quartile 3	3.87 (3.23, 4.51)	4.16 (3.57, 4.75)	4.27 (1.18, 7.17)	4.20 (3.99, 4.41)	2.98 (2.52, 3.45)	
Quartile 4	3.96 (3.32, 4.61)	4.06 (3.47, 4.66)	4.70 (1.78, 7.62)	4.34 (4.13, 4.54)	2.91 (2.44, 3.37)	
P-Value ⁴	0.57	0.66	0.79	0.07	0.48	
Per 1 unit increase	0.405 (0.094, 0.716)	0.038 (-0.364, 0.442)	0.466 (-0.468, 1.40)	1.16 (0.687, 1.64)	0.326 (0.079, 0.523)	0.54
P-Value	0.01	0.85	0.33	<0.001	0.01	
D6D (ratio)						
Fasting glucose						0.07
Quartile 1	0.0093 (0.0079, 0.0107)	0.0104 (0.0083, 0.0125)	0.0106 (0.0067, 0.0145)	0.0093 (0.0082, 0.0104)	0.0093 (0.0071, 0.0114)	

	Overall N=6,186	White N=2,407	Black N=1,634	Chinese N=770	Hispanic N=1,375	P-int ³
	LMeans/p (95% CI) ^{1,2}	LMeans/p (95% CI) ^{1,2}	LMeans/p (95% CI) ^{1,2}	LMeans/p (95% CI) ^{1,2}	LMeans/p (95% CI) ^{1,2}	
Quartile 2	0.0093 (0.0079, 0.0107)	0.0098 (0.0077, 0.0119)	0.0110 (0.0071, 0.0149)	0.0092 (0.0084, 0.0100)	0.0104 (0.0083, 0.0125)	
Quartile 3	0.0096 (0.0082, 0.0109)	0.0103 (0.0081, 0.0124)	0.0109 (0.0070, 0.0147)	0.0098 (0.0090, 0.0106)	0.0100 (0.0079, 0.0121)	
Quartile 4	0.0091 (0.0077, 0.0105)	0.0097 (0.0076, 0.0119)	0.0104 (0.0065, 0.0142)	0.0090 (0.0083, 0.0098)	0.0100 (0.0079, 0.0121)	
P-Value ⁴	0.50	0.06	0.66	0.68	0.11	
Per 1 unit increase	-0.0067 (-0.0013, -0.0000)	-0.0015 (-0.0298, -0.0001)	-0.0001 (-0.0013, 0.0012)	-0.0022 (-0.0040, -0.0004)	-0.0002 (-0.0013, 0.0009)	0.55
P-Value	0.05	0.04	0.92	0.02	0.71	

Abbreviations: LA: Linoleic Acid; GLA: Gamma-Linolenic Acid; DGLA: Dihomo-Gamma-Linolenic Acid; AA: Arachidonic Acid; DSD: Estimated delta-5 desaturase activity (AA/DGLA); D6D: Estimated delta-6 desaturase activity (GLA/LA); int: interaction; PUFA: polyunsaturated fatty acid.

¹Linear regression with fasting glucose modeled as the predictor adjusted for age, race/ethnicity, gender, waist circumference, education level, hypertension medication use, cigarette smoking, alcohol intake

²L-Smean N6-PUFAs for categorical evaluation of fasting glucose, β per 1 unit change in fasting glucose evaluated continuously.

³Test for interaction assessed by inclusion of cross-product term in multivariable adjusted model.

⁴Quartile 4 versus quartile 1.

⁵Quartile cut-points for fasting glucose: 83.0, 90.0, 99.0

Table 6.

Baseline omega-6 polyunsaturated fatty acid levels and estimated desaturase activity and diabetes incidence (through 2015) overall and by race/ethnicity (N=5,508) with adjustment for HOMA-IR.

	Overall			White			Black			Chinese			Hispanic		
	N cases/N total	HR (95% CI) ^{1,5}	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total
LA (18:2n6) ³															
Quartile 1	183/1358	Reference	74/615	Reference	73/496	Reference	8/46	Reference	8/46	Reference	28/201	Reference	28/201	Reference	28/201
Quartile 2	153/1380	0.80 (0.64, 1.00)	46/639	0.60 (0.41, 0.87)	55/397	0.94 (0.66, 1.34)	7/92	0.94 (0.66, 1.34)	7/92	0.33 (0.12, 0.94)	45/252	1.15 (0.71, 1.86)	45/252	1.15 (0.71, 1.86)	45/252
Quartile 3	163/1391	0.91 (0.73, 1.13)	52/597	0.85 (0.59, 1.23)	42/316	0.93 (0.63, 1.37)	19/154	0.93 (0.63, 1.37)	19/154	0.51 (0.21, 1.21)	50/324	1.14 (0.70, 1.85)	50/324	1.14 (0.70, 1.85)	50/324
Quartile 4	136/1379	0.67 (0.43, 0.86)	26/451	0.54 (0.34, 0.85)	13/154	0.56 (0.31, 1.02)	45/386	0.56 (0.31, 1.02)	45/386	0.48 (0.22, 1.05)	52/388	0.88 (0.54, 1.42)	52/388	0.88 (0.54, 1.42)	52/388
P-Value ²		0.002		0.008		0.06		0.06		0.06		0.60		0.60	
Continuous ⁴	635/5508	0.87 (0.80, 0.95)	198/2302	0.82 (0.69, 0.97)	183/1363	0.87 (0.73, 1.04)	79/678	0.87 (0.73, 1.04)	79/678	0.83 (0.67, 1.03)	175/1165	0.95 (0.80, 1.11)	175/1165	0.95 (0.80, 1.11)	175/1165
P-Value		0.003		0.02		0.13		0.13		0.09		0.50		0.50	
GLA (18:3n6) ³															
Quartile 1	138/1423	Reference	36/454	Reference	45/367	Reference	32/326	Reference	32/326	Reference	25/276	Reference	25/276	Reference	25/276
Quartile 2	159/1371	1.12 (0.89, 1.41)	49/536	0.91 (0.59, 1.41)	55/496	1.08 (0.72, 1.60)	14/140	1.08 (0.72, 1.60)	14/140	0.95 (0.50, 1.79)	41/299	1.42 (0.85, 2.37)	41/299	1.42 (0.85, 2.37)	41/299
Quartile 3	151/1338	1.03 (0.81, 1.31)	47/627	0.62 (0.40, 0.96)	42/337	0.80 (0.52, 1.23)	14/100	0.80 (0.52, 1.23)	14/100	1.32 (0.68, 2.53)	48/274	1.97 (1.19, 3.25)	48/274	1.97 (1.19, 3.25)	48/274
Quartile 4	187/1376	1.16 (0.92, 1.46)	66/685	0.70 (0.46, 1.07)	41/263	1.05 (0.62, 1.61)	19/112	1.05 (0.62, 1.61)	19/112	1.32 (0.72, 2.42)	61/316	1.92 (1.18, 3.13)	61/316	1.92 (1.18, 3.13)	61/316
P-Value ²		0.21		0.10		0.84		0.84		0.36		0.009		0.009	
Continuous ⁴	635/5508	1.05 (0.97, 1.14)	198/2302	0.88 (0.75, 1.04)	183/1363	1.02 (0.85, 1.22)	79/678	1.02 (0.85, 1.22)	79/678	1.19 (0.97, 1.45)	175/1165	1.19 (1.03, 1.37)	175/1165	1.19 (1.03, 1.37)	175/1165
P-Value		0.24		0.14		0.86		0.86		0.10		0.02		0.02	
DGLA (20:3n6) ³															
Quartile 1	104/1383	Reference	28/535	Reference	47/442	Reference	22/287	Reference	22/287	Reference	7/120	Reference	7/120	Reference	7/120
Quartile 2	124/1378	0.95 (0.73, 1.24)	35/585	0.97 (0.58, 1.62)	52/428	0.79 (0.53, 1.19)	23/170	0.79 (0.53, 1.19)	23/170	1.38 (0.75, 2.55)	14/195	1.19 (0.45, 3.11)	14/195	1.19 (0.45, 3.11)	14/195
Quartile 3	184/13751	1.14 (0.89, 1.47)	56/588	1.07 (0.66, 1.72)	56/317	0.93 (0.62, 1.40)	20/141	0.93 (0.62, 1.40)	20/141	1.31 (0.68, 2.54)	52/329	1.86 (0.79, 4.38)	52/329	1.86 (0.79, 4.38)	52/329
Quartile 4	223/1371	1.26 (0.97, 1.63)	79/594	1.18 (0.73, 1.90)	28/176	0.79 (0.48, 1.30)	14/80	0.79 (0.48, 1.30)	14/80	1.47 (0.72, 3.01)	102/521	2.21 (0.96, 5.13)	102/521	2.21 (0.96, 5.13)	102/521

	Overall			White			Black			Chinese			Hispanic		
	N cases/N total	HR (95% CI) ^{1,5}	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total	HR (95% CI) ¹	N cases/N total
P-Value ²		0.09		0.51		0.36		0.29		0.06		0.29		0.06	
Continuous ⁴	635/5508	1.17 (1.07, 1.27)	198/2302	1.10 (0.94, 1.28)	183/1363	1.01 (0.80, 1.28)	79/678	1.15 (0.92, 1.45)	175/1165	1.34 (1.14, 1.58)					
P-Value		<0.001		0.24		0.93		0.22		<0.001				<0.001	
AA (20:4n6) ³															
Quartile 1	135/1427	Reference	48/648	Reference	12/105	Reference	27/288	Reference	48/386	Reference				Reference	
Quartile 2	146/1399	1.13 (0.89, 1.44)	46/649	0.82 (0.54, 1.23)	28/259	1.10 (0.56, 2.18)	24/202	1.51 (0.84, 2.73)	48/289	1.46 (0.96, 2.21)					
Quartile 3	165/1378	1.26 (1.00, 1.60)	53/594	1.00 (0.67, 1.49)	49/382	1.36 (0.72, 2.58)	24/129	2.54 (1.41, 4.59)	39/273	1.09 (0.69, 1.73)					
Quartile 4	189/1304	1.54 (1.21, 1.96)	51/411	1.60 (1.06, 2.40)	94/617	1.57 (0.85, 2.91)	4/59	1.28 (0.43, 3.78)	40/217	1.43 (0.93, 2.22)					
P-Value ²		<0.001		0.02		0.15		0.66		0.11					
Continuous ⁴	635/5508	1.15 (1.06, 1.25)	198/2302	1.11 (0.95, 1.30)	183/1363	1.27 (1.08, 1.48)	79/678	1.25 (0.94, 1.65)	175/1165	1.08 (0.92, 1.26)					
P-Value		0.001		0.18		0.003		0.12		0.37					
D5D ³															
Quartile 1	197/1387	Reference	73/634	Reference	17/94	Reference	17/138	Reference	90/521	Reference					
Quartile 2	161/1410	0.87 (0.70, 1.08)	54/669	0.77 (0.54, 1.10)	23/235	0.59 (0.31, 1.13)	31/195	1.18 (0.65, 2.17)	53/311	1.08 (0.76, 1.54)					
Quartile 3	159/1484	0.97 (0.78, 1.22)	43/558	1.09 (0.73, 1.62)	69/435	1.12 (0.65, 1.92)	24/180	1.32 (0.69, 2.50)	23/211	0.66 (0.40, 1.08)					
Quartile 4	118/1327	0.97 (0.75, 1.26)	28/441	0.96 (0.60, 1.52)	74/599	1.19 (0.69, 2.05)	7/165	0.71 (0.29, 1.76)	9/122	0.72 (0.36, 1.45)					
P-Value ²		0.83		0.85		0.53		0.46		0.35					
Continuous ⁴	635/5508	0.98 (0.90, 1.06)	198/2302	0.98 (0.87, 1.11)	183/1363	1.01 (0.97, 1.06)	79/678	0.94 (0.77, 1.15)	175/1165	0.83 (0.67, 1.03)					
P-Value		0.57		0.75		0.55		0.57		0.10					
D6D ³															
Quartile 1	147/1367	Reference	31/376	Reference	68/490	Reference	26/257	Reference	22/244	Reference					
Quartile 2	156/1360	1.03 (0.82, 1.29)	50/539	0.97 (0.62, 1.54)	51/408	0.77 (0.43, 1.11)	17/160	1.02 (0.54, 1.91)	38/255	1.50 (0.87, 2.57)					
Quartile 3	151/1376	0.90 (0.71, 1.13)	50/654	0.64 (0.40, 1.01)	38/281	0.85 (0.57, 1.27)	15/1298	0.96 (0.50, 1.84)	48/312	1.38 (0.82, 2.30)					
Quartile 4	181/1405	1.08 (0.86, 1.36)	67/733	0.71 (0.46, 1.10)	26/184	0.86 (0.54, 1.37)	21/134	0.95 (0.52, 1.76)	67/354	2.07 (1.26, 3.42)					
P-Value ²		0.51		0.13		0.86		0.88		0.004					

	Overall			White			Black			Chinese			Hispanic		
	N cases/N total	HR (95% CI) ¹	I ²	N cases/N total	HR (95% CI) ¹	I ²	N cases/N total	HR (95% CI) ¹	I ²	N cases/N total	HR (95% CI) ¹	I ²	N cases/N total	HR (95% CI) ¹	I ²
Continuous ⁴	635/5508	1.01 (0.92, 1.11)		198/2302	0.87 (0.73, 1.04)		183/1363	0.89 (0.71, 1.13)		79/678	1.16 (0.91, 1.48)		175/1165	1.17 (0.99, 1.37)	
P-Value		0.81			0.13			0.33			0.24			0.06	

Abbreviations: LA: Linoleic Acid; GLA: Gamma-Linolenic Acid; DGLA: Dihomo-Gamma-Linolenic Acid; AA: Arachidonic Acid; D5D: Estimated delta-5 desaturase activity (AA/DGLA); D6D: Estimated delta-6 desaturase activity (GLA/LA); HR: hazard ratio; PUFA: polyunsaturated fatty acid.

¹ Cox proportional hazards regression adjusted for age, race/ethnicity, gender, waist circumference, education level, hypertension medication use, cigarette smoking, alcohol intake, and HOMA-IR (log-transformed).

² Quartile 4 vs. quartile 1.

³ Quartile cut-points: LA:17.97, 20.06, 22.29; GLA:0.079, 0.107, 0.139; DLGA:2.586, 3.103, 3.696; AA:9.87, 11.56, 13.36; D5D:2.947, 3.745, 4.732; D6D: 0.00668, 0.00923, 0.0124.

⁴ Per 1 standard deviation change.

⁵ Test for interaction by race/ethnicity were evaluated by inclusion of a cross-product term in multivariable adjusted models. Interactions were statistically significant for D6D: P=0.04 (continuous only). All other interactions were not significant at the P<0.05 level.