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Circulating omega-7 fatty acids are differentially related to metabolic dysfunction and incident type II diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Aim. -—Determine whether plasma omega-7 vaccenic acid and palmitoleic acid levels are related to homeostasis model of insulin resistance scores and incident type II diabetes, and whether race/ethnicity modifies these associations.

Methods. -—Plasma phospholipid fatty acids were measured by gas chromatography with flame-ionization detection in Multi-Ethnic Study of Atherosclerosis participants. Linear regression determined associations of vaccenic acid and palmitoleic acid with log-transformed homeostasis model of insulin resistance scores (N=5689), and Cox regression determined associations with incident type II diabetes (N=5413, 660 cases). Race-interactions were tested.

Results. -—Adjusting for typical risk factors, higher levels of plasma vaccenic acid were found to be inversely associated with insulin resistance scores across all four race/ethnicities, and a significant race-interaction was observed between Hispanics and Caucasians (P for interaction = 0.03). Vaccenic acid was related to 17%, 32%, and 39% lower risks of incident type II diabetes in Black, Hispanic, and Chinese American participants, respectively. Differences in associations between races were detected (P for interactions < 0.05). By contrast, higher levels of plasma palmitoleic acid were related to greater insulin resistance scores in Blacks (P < 0.001) and Hispanics (P < 0.001); significant race-based differences between associations were detected (P

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DISCLOSURES

The authors have no competing interests to disclose.

for interactions < 0.05). Palmitoleic acid was correspondingly related to a 21% greater risk of incident type II diabetes in Black individuals.

Conclusions. -—Results suggest that plasma vaccenic acid and palmitoleic acid are markers of metabolic health and dysfunction, respectively. Coupled with previous evidence and the significant race interactions, our findings have implications for future studies of the race-based differences in omega-7 fatty acids and their regulation in the context of deteriorating metabolic health.

Keywords

Ethnicity; HOMA; MESA; Omega-7; Plasma fatty acid; Race; Type 2 diabetes

Introduction

Type 2 diabetes (T2D) and insulin resistance are characterized by metabolic dysfunction, most notably elevated blood glucose levels and protracted rates of glucose disposal. Furthermore, homeostasis of other nutrients and bioactive compounds are also disrupted—among these, bioavailable levels of fatty acids (FA). While elevated plasma saturated FAs have been well-described for predicting metabolic disease development including incident T2D [1–6], few large cohort studies have examined circulating levels of omega-7 cis-vaccenic acid and cis-palmitoleic acid in the context of metabolic health, and no studies have tested the likely modifying influence of race/ethnicity.

Plasma and tissue levels of palmitoleic acid and vaccenic acid are largely produced through de novo lipogenesis and regulated by numerous hormones including insulin [7]. Critically, de novo lipogenic dysregulation results in aberrant fatty acid levels [7], which, in turn, may predict future clinical outcomes. Prospective analyses have shown that lower plasma vaccenic acid levels are related to greater risk of incident T2D [1–2,8]—though null findings have also been reported [6,9]. By comparison, studies of palmitoleic acid have found opposing results. Elevated levels in humans have been shown to be associated with greater fasting glucose and insulin levels [10] as well as risk of T2D [1, 9, 11]. Conversely, cell culture and animal models of palmitoleic acid have shown that it promotes insulin sensitivity and suppresses pro-inflammatory stimuli that would otherwise disrupt insulin-signalling [12–13]. Taken together, evidence is equivocal as to whether vaccenic acid and palmitoleic acid may represent markers of metabolic health and disease, respectively, or otherwise have direct roles in insulin signalling.

In examining fatty acids and metabolic disease, race/ethnicity is likely an important modifying variable due to inherent race differences in both plasma fatty acid profiles [14] and prevalence of T2D [15]. Moreover, whether racial/ethnic differences in omega-7 fatty acid levels have implications in T2D development has not been studied in a multi-ethnic cohort. Overall, the aims of the present study were to determine whether plasma levels of cis-vaccenic acid and cis-palmitoleic acid are: 1) cross-sectionally related to insulin resistance based on the homeostasis model of insulin resistance (HOMA-IR); 2) prospectively related incident T2D over a 9.2 year follow up period; and 3) whether race-ethnicity may serve as a modifying variable for any observed associations.

Materials and Methods

Population

The primary aim of Multi-Ethnic Study of Atherosclerosis (MESA) is to investigate clinical and subclinical cardiovascular disease development and progression. The study design has been previously described [16], and information about MESA is available at http://www.mesa-nhlbi.org. MESA is composed of 6,814 men and women between the ages of 45 and 84 years and without evidence of clinical cardiovascular disease at baseline. The population of 38.6% White, 27.6% Black, 11.8% Chinese American, and 22.0% Hispanic subjects was recruited from six communities in the U.S. (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St. Paul, MN). Institutional Review Board approval was obtained at all MESA sites, and all participants gave informed consent. Recruitment and baseline examinations began in July 2000 and were conducted over a 24-month period. Participants with T2D at baseline and individuals with missing plasma phospholipid fatty acid or other covariate data were excluded resulting in a study sample of 5,714 participants.

Demographic and Anthropometric Characteristics

Information regarding age, sex, race/ethnicity, education, medication, and lifestyle factors was obtained by questionnaires. Height (m), weight (kg), and waist circumference **(cm)** were measured according to standard procedures [16].

Plasma and Serum Analytes

Twelve-hour fasting blood was drawn, and EDTA-anticoagulant tubes were collected and stored at −70°C using a standardized protocol [16]. All routine measurements were performed at the Advanced Research and Diagnostics Laboratory at the University of Minnesota (Minneapolis, MN). Serum insulin was measured by an immunoenzymatic sandwich assay (Beckman Access Immunoassay System, Beckman Coulter, Inter-assay CV: 4.9%) 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) using Centres for Disease Control and Prevention-standardized methods. Insulin resistance was examined using the homeostasis model assessment of insulin resistance (HOMA-IR) with the following equation: [fasting insulin (mIU/L) − fasting glucose (mmol/L)]/22.5.

Phospholipid fatty acid profiles were extracted from EDTA plasma at the first examination using the chloroform/methanol method previously described by Cao et al. [17]. Briefly, lipids are extracted with a mixture of chloroform/methanol (2:1, volume for volume) and subclasses are separated using thin-layer chromatography. The phospholipid band is harvested and derivatized to methyl esters. The final product is dissolved in heptane and injected onto a capillary Varian CP7420 100-m column with a Hewlett Packard 5890 gas chromatograph. The gas chromatograph is configured for a single capillary column with a flame ionization detector and interphased with HP chemstation software. Fatty acids were expressed as a percent of the total phospholipid fatty acid fraction. The following

coefficients of variation were obtained for cis-isomers of omega-7 fatty acids (n=150): vaccenic acid: 3.1%; palmitoleic acid: 4.1%.

Incident Type 2 Diabetes

Incident T2D was determined across 5 exams and 12 follow-up contacts over a median 9.2 years and was defined by one the following criteria: reported physician diagnosis, use of diabetes medications, or fasting (12-h) glucose >126 mg/dL.

Statistical Methods

Statistical analysis was conducted using Stata, version 15.0 (Stata Corp, College Station, TX). Log transformation of data was employed where distributions were skewed. Initial descriptive statistics for each fatty acid (expressed as a % of the total), participant demographic, lifestyle and clinical characteristics are presented as means (SD) or medians (inter-quartile range) for normally distributed and skewed continuous variables, respectively, and frequencies for categorical variables. Fatty acids were treated as continuous variables in the analyses (per SD, calculated from the entire cohort). They were also treated as quartiles in a sensitivity analysis, and linear trend tests were performed to examine linear trend across quartiles. Cox regression analysis determined fatty acid-associated risk of incident T2D over the study follow-up period with adjustment for demographic and lifestyle covariates. Residuals analyses were applied to check for model assumptions. Linear regression determined associations between each fatty acid and baseline HOMA-IR, adjusting for the same covariates. To examine differences in associations across race/ethnicity groups, interaction terms between fatty acids and race were tested in a joint 3-df chi-square test. As interaction were statistically significant ($P < 0.05$) in most analyses, we focused our report on race-stratified analyses. To correct for multiple testing in four groups, a P-value < 0.0125 (= 0.05/4, bonferroni correction) was considered statistically significant.

Results

Demographic, lifestyle, and clinical characteristics of MESA participants are stratified by baseline HOMA-IR scores and presented in Table I. Compared to those in the top quartile, individuals in the bottom quartile were more likely to be female, current consumers of alcohol, taking hypertension medication, attained a higher education, have a lower systolic blood pressure, BMI score, waist circumference, and greater levels of HDL-C and plasma vaccenic acid levels. Cohort characteristics were also stratified by incident T2D cases and non-cases, presented in Table II. Compared to non-cases, those who developed T2D over the median 9.2-year follow-up period had lower education level, were more likely to be taking blood pressure medication, have lower levels of HDL-C and plasma vaccenic acid, higher systolic blood pressure and BMI score, waist circumference, higher plasma palmitoleic acid levels, and greater baseline HOMA-IR scores.

Linear trend tests showed significant trends across quartiles of each fatty acid for both incident T2D and HOMA-IR score ($P < 0.001$); therefore, results were mainly reported for continuous fatty acids (per SD). Fatty acid-race interactions were first tested in the entire MESA cohort. For incident T2D, the interaction test (3df chi-square test) P-values were

0.0046 and 0.95 for vaccenic acid and palmitoleic acid, respectively; and for (log-transformed) HOMA-IR, the interaction *P*-values were 0.026 and 0.0002. As the interactions were statistically significant in 3 of the 4 analyses and to keep the report consistent, we showed race-stratified analysis while acknowledging that the magnitudes of association for palmitoleic acid and T2D were similar across race groups.

Race-stratified cross-sectional associations of plasma vaccenic acid and palmitoleic acid with baseline HOMA-IR scores are presented in Table III. After adjusting for age and sex, vaccenic acid levels (per SD) were inversely associated with log-HOMA-IR scores in Black (β = −0.18), Caucasian (β = −0.16), Chinese American (β = −0.20) and Hispanic individuals (β = −0.19) (all $P < 0.001$). As the HOMA-IR scores were log-transformed which leads to a multiplicative model in the original scale, these estimated coefficients approximately correspond to 16%, 15%, 18%, and 17% respective decrease in the original HOMA-IR scale per SD difference in vaccenic acid. In the fully adjusted model, associations were attenuated but remained significant in Black (β = −0.12), Caucasian (β = −0.09), Chinese American (β = −0.10) and Hispanic individuals (β = −0.11) (all $P < 0.001$), corresponding to ~12%, 9%, 10% and 11% respective decrease in HOMA-IR. Associations between Hispanics and Caucasians were statistically different, with a greater magnitude of association in Hispanic individuals (*P* for interaction = 0.0078 for Hispanic vs Caucasians).

In contrast to vaccenic acid, higher palmitoleic acid levels (per SD) were related to greater log-HOMA-IR scores in Black (β = 0.08; $P < 0.001$), Caucasian (β = 0.03; $P = 0.004$), and Hispanic individuals (β = 0.07; $P < 0.001$) corresponding to ~8%, 3%, and 7% respective increase in HOMA-IR. Associations were significantly different in Black participants compared to Caucasians (*P* for interaction < 0.001) and Chinese Americans (*P* for interaction = 0.006); and in Hispanics compared to Caucasians (*P* for interaction = 0.003) and Chinese Americans (*P* for interaction = 0.02). In the fully adjusted model, associations were attenuated except for Black participants (β = 0.070; $P < 0.001$) and Hispanic participants (β = 0.053; $P < 0.001$), corresponding to a ~7% and 5% increased HOMA-IR, and were rendered non-significant in Caucasians. Significant race-interactions remained in Black participants compared to Caucasians (*P* for interaction = 7.4×10^{-4}) and Hispanics vs Caucasians (*P* for interaction = 0.028).

Race-stratified associations of vaccenic acid and palmitoleic acid with risk of incident T2D over a median 9.2-year follow-up are presented in Table IV. The incidence rate was approximately 16 per 1000 person-years. After adjustment for age and sex, higher baseline levels of vaccenic acid (per SD) were associated with respective 26%, 21%, 52%, and 39% lower risks of incident T2D in Black, Caucasian, Chinese American, and Hispanic participants. Chinese American participants exhibited the nominally lowest risk of disease incidence per SD of vaccenic acid ($P < 0.001$), and associations with T2D were significantly different in Chinese American participants than those of Black (*P* for interaction = 0.006) and Caucasian participants (*P* for interaction < 0.001) as well as for Hispanics participants compared to those of Caucasians (*P* for interaction = 0.002). In the fully adjusted model, higher baseline levels of vaccenic acid remained significantly associated with respective 17%, 39%, and 32% lower risks of T2D in Black ($P = 0.019$), Chinese American ($P < 0.001$), and Hispanic ($P < 0.001$) participants, but the association was rendered non-

significant in Caucasians. The nominally lowest risk remained in Chinese Americans, and the association was different than those of Black (P for interaction = 0.01) and Caucasian participants (P for interaction = 0.001). The race-interaction also remained significant between Hispanics and Caucasians (P for interaction = 0.018).

In contrast to vaccenic acid, higher levels of palmitoleic acid (per SD) were related to 18% and 22% greater risks of incident T2D in Black (P = 0.05) and Caucasian participants (P = 0.001), respectively, following adjustment for age and sex. In the fully adjusted model, the association stayed similar in Black individuals with a 21% increase in risk (P = 0.031), but became marginally significant in Caucasians (P = 0.057). Considering multiple hypothesis tests in 4 race/ethnicity groups, both p-values were not statistically significant in the full model. No race-interactions in either model were observed (P > 0.05).

Demographic, lifestyle, and clinical characteristics of MESA participants are stratified by race/ethnicity and presented in Table S1; see supplementary material associated with this article on line. Individuals with prevalent T2D, missing exposure variables, or missing covariates were excluded. Significant race-/ethnicity-based differences were observed. Among these, Black participants were found to have the highest mean BMI scores and the lowest mean levels of both palmitoleic acid and vaccenic acid. Caucasians had the lowest median HOMA-IR scores and the highest mean levels of plasma palmitoleic acid. Chinese Americans were shown to have the lowest mean BMI scores and highest mean levels of plasma vaccenic acid. Finally, Hispanics were found to have the highest median HOMA-IR scores. For T2D, Hispanic (14.9%) and Black individuals (13.7%) were found to have higher incidence rates than Chinese Americans (11.8%) or Caucasians (8.5%).

Discussion

In this multi-ethnic cohort of MESA participants free of T2D at baseline, omega-7 cis-vaccenic acid and cis-palmitoleic acid were found to be differentially associated with HOMA-IR scores and risk of incident T2D over a median 9.2-year follow-up (or 41,859 person-years). Plasma palmitoleic acid levels were positively and independently associated with HOMA-IR scores in Black and Hispanic individuals and were further related to a 21% greater risk of incident T2D in Black participants alone in the fully adjusted model. By contrast, plasma vaccenic acid levels were inversely associated with HOMA-IR score across all races and related to 17%, 39%, and 32% lower risks of incident T2D in Black, Chinese American, and Hispanic participants, respectively. No significant association with T2D risk was observed in Caucasians. Significant differences in associations were observed between races/ethnicities.

Until recently, only a handful of studies have interrogated cis-vaccenic acid and metabolic outcomes, but evidence is mounting that higher levels are related to healthier metabolic profiles and lower risks of T2D development. In observational studies, vaccenic acid has been shown to be related to greater insulin sensitivity and beta-cell function in a recent prospective analysis [18]. Cohort study participants in the top tertiles of vaccenic acid have also been shown to be at 60% and 45% lower risks to develop T2D compared to those in bottom tertiles in EPIC-Norfolk [1] and Cardiovascular Health Study [8], respectively. Yet,

null findings have been reported in EPIC-Potsdam [6] and Metabolic Syndrome in Men study cohorts [9] as well as in a cross-sectional study of 176 Hispanic and Caucasian individuals (n=176) [19]. Yet these latter two studies were likely underpowered. In the Metabolic Syndrome in Men cohort study, only 30 cases of T2D occurred over the follow up period, while the cross sectional analysis was comprised of 56 control subjects, 61 pre-diabetes cases, and 59 diabetes cases. Finally, the EPIC-Postdam case-cohort study was well-powered with 673 incident cases of T2D over a mean follow up period of 7 years, and the underlying reason(s) for the disparate findings between the EPIC-Potsdam study and our analysis as well as other cohort studies that reported significant associations is unclear.

Overall, the present analysis supports an independent relationship of vaccenic acid with lower HOMA-IR scores and risk of incident T2D, and we extend previous findings by showing significant differences in associations with T2D between Chinese American and Caucasians participants (P for interaction = 0.001) as well as Chinese American and Black participants (P for interaction = 0.01). Based on the strength of these interactions and the null finding in Caucasians, it may be speculated that vaccenic acid is a stronger marker of metabolic health in Chinese Americans compared to Black or Caucasian individuals or has a greater protective influence in Chinese American individuals. Importantly, vaccenic acid levels are largely derived from fatty acid synthesis and the enzymatic activity of elongase-5. Elongase-5 activity has been shown to reduce blood glucose and insulin levels in mouse obesity models [20–21] and suppress delta-9 desaturase activity [22]—with the latter also shown to result in lower insulin resistance in rodents [23]. These findings suggest that higher vaccenic acid levels may be concomitant with elevated elongase-5 activity, lower desaturase activity, and an enhanced metabolic profile. It may be speculated that greater elongase activity may contribute to the higher levels of plasma vaccenic acid levels and their stronger associations with HOMA-IR and T2D in Chinese American participants compared to other races/ethnicities. Since this is the first time that race/ethnicity has been shown to be an important modifying variable for omega-7 FAs, additional multi-ethnic cohort studies are needed for confirmation and to further interrogate cis-vaccenic acid, elongase-5, and potential environmental and genetic factors that influence their regulation across race/ethnicity.

Compared to studies of vaccenic acid, those of palmitoleic acid suggest a more complex interplay between its circulating concentrations, origin of synthesis, and potential for metabolic health benefits or detriments. Animal and cell culture models have largely demonstrated that palmitoleic acid has metabolic benefits—e.g., it promotes enhanced beta cell function [24] and suppresses inflammatory cytokine production [12]. And yet, observational studies in humans have shown that palmitoleic acid is related to greater T2D risk [1,5,9, 11, 25–26]—though null findings have also been reported [8, 27–29]. This apparent dichotomy between human and animal model studies may reflect the differential origins of palmitoleic acid synthesis as proposed by Mozaffarian et al. [10]. In humans, higher levels of plasma phospholipid palmitoleic acid levels are likely the result of up-regulated hepatic synthesis promoted by an unhealthy lifestyle: hypercaloric intake, little or no physical activity, adiposity, or excessive alcohol consumption [30–35]. In addition, it may be speculated that reduced activity of hepatic elongase-5 also results in higher palmitoleic acid levels, lower vaccenic acid levels, and contributes to metabolic dysfunction. By

contrast, higher levels of palmitoleic acid in rodents may be driven by proportionally greater synthesis in adipose tissue, which has been proposed to result in greater insulin sensitivity [13]. Ultimately, there remain a number of open questions regarding palmitoleic acid that are beyond the scope of cohort-based research; we propose that hepatic- and adipose-derived palmitoleic acid represent markers of (or have direct roles in) metabolic dysregulation and metabolic health, respectively, and further studies are warranted.

Overall, our results are consistent with studies showing palmitoleic acid to be a marker of metabolic dysfunction and independent risk factor for T2D, but we further observed that race/ethnicity was an important modifying variable for associations with HOMA-IR, which may explain the variation among previous study results. Similar to vaccenic acid, the observed race interactions may reflect race-based differences in palmitoleic acid, its origin of synthesis, and its regulation by desaturase and elongase activities. Ultimately, the observed associations and novel race interactions underscore the need for further research to examine genetic and environmental factors that disrupt its homeostasis across different races/ethnicities.

This prospective examination of a large multi-ethnic cohort has a number of strengths as well as limitations. The 5414 individuals and 665 incident T2D cases in fully adjusted models provided robust statistical power to detect associations and multiple significant race-interactions. Measurements of plasma phospholipid fatty acids served as objective measures of vaccenic and palmitoleic acids, and their respective 3.1% and 4.1% coefficients of variation indicate acceptable analytical precision. While our cross-sectional findings cannot establish causation, the prospective findings and 9.2-year follow-up period allowed for the scrutiny of temporality of associations between plasma fatty acids and T2D incidence. In terms of limitations, these results may not be generalizable to other populations since MESA is a U.S.-based cohort. In addition, statistical models were adjusted for typical covariates, but other lifestyle and risk exposures that were not evaluated across different race/ethnic groups likely remain, and the presence of residual confounding cannot be excluded.

In summary, our results indicate that plasma levels of cis-vaccenic acid and cis-palmitoleic acid are independent markers of metabolic health and dysfunction in humans, respectively. Coupled with the significant race-based differences in associations, our findings have implications for future studies of these omega-7 fatty acids, their synthesis, and the disruption of their homeostasis with deteriorating metabolic health, which may partially contribute to differences in T2D development across race/ethnicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

[1]. Patel PS, Sharp SJ, Jansen E, Luben RN, Khaw KT, Wareham NJ, et al. Fatty acids measured in plasma and erythrocyte-membrane phospholipids and derived by food-frequency questionnaire and the risk of new-onset type 2 diabetes: a pilot study in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort. Am J Clin Nutr 2010;92:1214–22. [PubMed: 20861175]

[2]. Forouhi NG, Imamura F, Sharp SJ, Koulman A, Schulze MB, Zheng J, et al. Association of Plasma Phospholipid n-3 and n-6 Polyunsaturated Fatty Acids with Type 2 Diabetes: The EPIC-InterAct Case-Cohort Study. PLoS Med 2016;13:e1002094. [PubMed: 27434045]

[3]. Wu JHY, Micha R, Mozafarrian D. Dietary fats and cardiometabolic disease: mechanisms and effects on risk factors and outcomes. Nat Rev Cardiol 2019 [Epub ahead of print].

[4]. Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH; ARIC Study Investigators. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2003;78:91–8. [PubMed: 12816776]

[5]. Hodge AM, English DR, O'Dea K, Sinclair AJ, Makrides M, Gibson RA, et al. Plasma phospholipid and dietary fatty acids as predictors of type 2 diabetes: interpreting the role of linoleic acid. Am J Clin Nutr 2007;86:189–97. [PubMed: 17616780]

[6]. Kroger J, Zietemann V, Enzenbach C, Weikert C, Jansen EH, Doring F, et al. Erythrocyte membrane phospholipid fatty acids, desaturase activity, and dietary fatty acids in relation to risk of type 2 diabetes in the European Prospective Investigation in to Cancer and Nutrition (EPIC)-Potsdam Study. Am J Clin Nutr 2011; 93:127–42. [PubMed: 20980488]

[7]. Ameer F, Scandiuzzi L, Hasnain S, Kalbacher H, Zaidi N. De novo lipogenesis in health and disease. Metabolism 2014;63:895–902. [PubMed: 24814684]

[8]. Ma W, Wu JH, Wang Q, Lemaitre RN, Mukamal KJ, Djoussé L, et al. Prospective association of fatty acids in the de novo lipogenesis pathway with risk of type 2 diabetes: the Cardiovascular Health Study. Am J Clin Nutr 2015;101:153–63. [PubMed: 25527759]

[9]. Mahendran Y, Agren J, Uusitupa M, Cederberg H, Vangipurapu J, Stancakova A, et al. Association of erythrocyte membrane fatty acids with changes in glycemia and risk of type 2 diabetes. Am J Clin Nutr 2014;99:79–85. [PubMed: 24153340]

[10]. Wu JHY, Micha R, Mozaffarian D. Dietary fats and cardiometabolic disease: mechanisms and effects on risk factors and outcomes. Nat Rev Cardiol 2019 [Epub ahead of print]

[11]. Zong G, Zhu Z, Sun L, Ye X, Lu L, Jim Q, et al. Associations of erythrocyte fatty acids in the de novo lipogenesis pathway with risk of metabolic syndrome in a cohort study of middle-aged and older Chinese. Am J Clin Nutr 2013;98:319–26. [PubMed: 23803879]

[12]. Guo X, Li H, Xu H, Halim V, Zhang W, Wang H, et al. Palmitoleate induces hepatic steatosis but suppresses liver inflammatory response in mice. PLoS One 2012;7:e39286. [PubMed: 22768070]

[13]. Cao H, Gerhold K, Mayers JR, Wiest MM, Watkins SM, Hotamisligil GS. Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. Cell 2008;134:933–44. [PubMed: 18805087]

[14]. Steffen BT, Steffen LM, Tracy R, Siscovick D, Jacobs D, Liu K, et al. Ethnicity, plasma phospholipid fatty acid composition and inflammatory/endothelial activation biomarkers in the Multi-Ethnic Study of Atherosclerosis (MESA). Eur J Clin Nutr 2012;66:600–5. [PubMed: 22215136]

[15]. Spanakis EK, Golden SH. Race/ethnic difference in diabetes and diabetic complications. Curr Diab Rep 2013;13:814–23. [PubMed: 24037313]

[16]. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AP et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81. [PubMed: 12397006]

[17]. Cao J, Schwichtenberg KA, Hanson NQ, Tsai MY. Incorporation and clearance of omega-3 fatty acids in erythrocyte membranes and plasma phospholipids. Clin Chem 2006;52:2265–72. [PubMed: 17053155]

[18]. Johnston LW, Harris SB, Retnakaran R, Zinman B, Giacca A, Liu Z, et al. Longitudinal associations of phospholipid and cholesteryl ester fatty acids with disorders underlying diabetes. J Clin Endocrinol Metab 2016;101:2536–44. [PubMed: 27144932]

[19]. Chuang LT, Glew RH, Li CC, VanderJagt DJ, Broyles JS, Ray GM, et al. Comparison of the fatty acid composition of the serum phospholipids of controls, prediabetics and adults with type 2 diabetes. J Diabetes Mellitus 2012;2:393–401. [PubMed: 25414798]

[20]. Tripathy S, Torres-Gonzalez M, Jump DB. Elevated hepatic fatty acid elongase-5 activity corrects dietary fat-induced hyperglycemia in obese C57BL/6J mice. J Lipid Res 2010;51:2642–54. [PubMed: 20488798]

[21]. Tripathy S, Jump DB. Elovl5 regulates the mTORC2-Akt-FOXO1 pathway by controlling hepatic cis-vaccenic acid synthesis in diet-induced obese mice. J Lipid Res 2013;54:71–84. [PubMed: 23099444]

[22]. Wang Y, Botolin D, Xu J, Christian B, Mitchell E, Jayaprakasam B, et al. Regulation of hepatic fatty acid elongase and desaturase expression in diabetes and obesity. J Lipid Res 2006;47:2028–41. [PubMed: 16790840]

[23]. Alstrup KK, Gregersen S, Jensen HM, Thomsen JL, Hermansen K. Differential effects of cis and trans fatty acids on insulin release from isolated mouse islets. Metabolism 1999;48:22–9. [PubMed: 9920140]

[24]. Maedler K, Spinas GA, Dyntar D, Moritz W, Kaiser N, Donath MY. Distinct effects of saturated and monounsaturated fatty acids on beta-cell turnover and function. Diabetes 2001;50:69–76. [PubMed: 11147797]

[25]. Krachler B, Norberg M, Eriksson JW, Hallmans G, Johansson I, Vessby B, et al. Fatty acid profile of the erythrocyte membrane preceding development of Type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis 2008;18:503–10. [PubMed: 18042359]

[26]. Vessby B, Aro A, Skarfors E, Berglund L, Salminen I, Lithell H. The risk to develop NIDDM is related to the fatty acid composition of the serum cholesterol esters. Diabetes 1994;43:1353–7. [PubMed: 7926311]

[27]. Laaksonen DE, Lakka TA, Lakka HM, Nyyssönen K, Rissanen T, Niskanen LK, et al. Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. Diabet Med 2002;19:456–64. [PubMed: 12060056]

[28]. Lankinen MA, Stančáková A, Uusitupa M, Ågren J, Pihlajamäki J, Kuusisto J, et al. Plasma fatty acids as predictors of glycaemia and type 2 diabetes. Diabetologia 2015;58:2533–44. doi:10.1007/s00125-015-3730-5. Epub 2015 Aug 16. [PubMed: 26277381]

[29]. Mozaffarian D, Cao H, King IB, Lemaitre RN, Song X, Siscovick DS, et al. Circulating palmitoleic acid and risk of metabolic abnormalities and new-onset diabetes. Am J Clin Nutr 2010;92:1350–8. [PubMed: 20943795]

[30]. Hudgins LC, Hellerstein M, Seidman C, Neese R, Diakun J, Hirsch J. Human fatty acid synthesis is stimulated by a eucaloric low fat, high carbohydrate diet. J Clin Invest 1996;97:2081–91. [PubMed: 8621798]

[31]. Marques-Lopes I, Ansorena D, Astiasaran I, Forga L, Martinez JA. Postprandial de novo lipogenesis and metabolic changes induced by a high-carbohydrate, low-fat meal in lean and overweight men. Am J Clin Nutr 2001;73:253–61. [PubMed: 11157321]

[32]. Schwarz JM, Linfoot P, Dare D, Aghajanian K. Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenergetic diets. Am J Clin Nutr 2003;77:43–50. [PubMed: 12499321]

[33]. King IB, Lemaitre RN, Kestin M. Effect of a low-fat diet on fatty acid composition in red cells, plasma phospholipids, and cholesterol esters: investigation of a biomarker of total fat intake. Am J Clin Nutr 2006;83:227–36. [PubMed: 16469979]

[34]. Hudgins LC, Baday A, Hellerstein MK, Parker TS, Levine DM, Seidman CE et al. The effect of dietary carbohydrate on genes for fatty acid synthase and inflammatory cytokines in adipose tissues from lean and obese subjects. J Nutr Biochem 2008;19:237–45. [PubMed: 17618104]

[35]. Chong MF, Hodson L, Bickerton AS, Roberts R, Neville M, Karpe F et al. Parallel activation of de novo lipogenesis and stearoyl-CoA desaturase activity after 3 d of high-carbohydrate feeding. Am J Clin Nutr 2008;87:817–23. [PubMed: 18400702]

Table I.

Demographic, lifestyle, and clinical characteristics of Multi-Ethnic Study of Atherosclerosis participants stratified by quartiles of baseline HOMA-IR score. Individuals with prevalent diabetes or missing covariates were excluded.

	Quartile of HOMA-IR				
Variable	**1**	**2**	**3**	**4**	***P*-value**
N	1482	1478	1480	1480	
Baseline HOMA-IR, median (IQR)	0.99 (0.83, 1.1)	1.5 (1.3, 1.6)	2.1 (1.9, 2.4)	3.6 (3.0, 4.6)	
Log HOMA-IR, mean (SD)	−0.066 (0.22)	0.38 (0.10)	0.76 (0.12)	1.35 (0.31)	
Age, mean (SD)	61.7 (10.5)	62.0 (10.4)	62.1 (10.6)	61.4 (9.7)	NS
Sex, n (% Female)	840 (56.7)	808 (54.7)	772 (52.2)	751 (50.7)	0.006
Education, n (%)					< 0.001
<High School	174 (11.7)	238 (16.1)	269 (18.2)	284 (19.2)	
Completed High School/GED	224 (15.2)	251 (17.1)	277 (18.8)	306 (20.7)	
Some College <4 year Degree	394 (26.6)	418 (28.3)	430 (29.1)	450 (30.4)	
Bachelor's Degree	326 (22.1)	258 (17.6)	247 (16.7)	230 (15.6)	
Graduate Or Professional School	357 (24.2)	304 (20.7)	254 (17.2)	208 (14.1)	
Race/ethnicity					< 0.001
Black	360 (24.3)	341 (23.1)	392 (26.5)	451 (30.5)	
Caucasian	763 (51.5)	630 (42.6)	575 (38.9)	484 (32.7)	
Chinese American	138 (9.3)	220 (14.9)	194 (13.1)	143 (9.7)	
Hispanic	221 (14.9)	287 (19.4)	319 (21.6)	402 (27.2)	
Smoking status, n (%)					NS
Former	553 (37.5)	517 (35.2)	532 (36.0)	555 (37.6)	
Current	205 (13.9)	197 (13.4)	186 (12.6)	178 (12.0)	
Alcohol consumption status, n (%)					< 0.001
Former	270 (18.4)	325 (22.2)	334 (22.7)	390 (26.5)	
Current	966 (65.8)	843 (57.5)	822 (55.9)	774 (52.5)	
Systolic blood pressure, mean (SD)	121.4 (21.5)	123.7 (21.5)	127.2 (20.7)	130.4 (20.1)	< 0.001
Hypertension Medication, n (%)	360 (24.3)	417 (28.2%)	540 (36.5)	658 (44.5)	< 0.001
Body Mass Index (kg/m^2), mean (SD)	24.7 (3.9)	26.7 (4.4)	28.9 (4.8)	31.7 (5.4)	< 0.001
Waist Circumference (cm), mean (SD)	**87.8 (11.2)**	**94.1 (11.9)**	**99.8 (12.3)**	**107.0 (13.3)**	**< 0.001**
Total cholesterol (mg/dL), mean (SD)	193.5 (33.1)	195.5 (34.69)	197.0 (36.2)	193.8 (36.1)	0.02
HDL-C (mg/dL), mean (SD)	58.9 (16.6)	53.7 (14.5)	49.1 (13.1)	45.0 (11.4)	< 0.001
Plasma fatty acids (% of total)					
Vaccenic acid, mean (SD)	1.47 (0.26)	1.41 (0.23)	1.35 (0.23)	1.27 (0.21)	< 0.001
Palmitoleic acid, mean (SD)	0.52 (0.26)	0.50 (0.24)	0.51 (0.24)	0.53 (0.23)	0.01

Definitions: HOMA-IR: homeostasis model assessment of insulin resistance

Table II.

Demographic, lifestyle, and clinical characteristics of Multi-Ethnic Study of Atherosclerosis participants stratified by cases and non-cases of incident type II diabetes. Individuals with prevalent diabetes or missing covariates were excluded.

Variable	Cases	Non-cases	*P*-value
N	695	5234	
Age, mean (SD)	60.8 (9.5)	61.9 (10.4)	0.007
Sex, n (% Female)	361 (51.9)	2816 (53.8)	NS
Education, n (%)			0.03
<High School	135 (19.5)	830 (15.9)	
Completed High School/GED	135 (19.5)	925 (17.7)	
Some College <4 year Degree	208 (30.0)	1487 (28.4)	
Bachelor's Degree	97 (14.0)	965 (18.5)	
Graduate Or Professional School	119 (17.1)	1007 (19.3)	
Race/ethnicity			< 0.001
Black	216 (31.1)	1333 (25.5)	
Caucasian	210 (30.2)	2244 (42.9)	
Chinese American	82 (11.8)	614 (11.7)	
Hispanic	187 (26.9)	1043 (19.9)	
Smoking status, n (%)			NS
Former	258 (37.2)	1901 (36.5)	
Current	84 (12.1)	685 (13.1)	
Alcohol consumption status, n (%)			NS
Former	168 (24.3)	1155 (22.2)	
Current	375 (54.2)	3032 (58.4)	
Systolic blood pressure, mean (SD)	130.0 (20.5)	125.1 (21.3)	< 0.001
Blood pressure medication, n (%)	307 (44.2)	1670 (31.9)	< 0.001
Body mass index (kg/m^2), mean (SD)	31.1 (5.8)	27.6 (5.2)	< 0.001
Waist Circumference (cm), mean (SD)	**105.0 (14.1)**	**96.1 (13.8)**	**< 0.001**
Total cholesterol (mg/dL), mean (SD)	194.2 (36.3)	195.0 (34.9)	NS
HDL-C (mg/dL), mean (SD)	46.7 (12.2)	52.4 (15.2)	< 0.001
Plasma fatty acids (% of total)			
Vaccenic acid, mean (SD)	1.29 (0.21)	1.38 (0.25)	< 0.001
Palmitoleic acid, mean (SD)	0.54 (0.25)	0.51 (0.24)	0.02
Baseline HOMA-IR, median (IQR)	2.93 (1.97, 4.15)	1.65 (1.19, 2.42)	< 0.001

Definitions: HOMA-IR: homeostasis model assessment of insulin resistance

Table III.

Race-stratified linear regression analysis of plasma vaccenic acid (18:1n7c) and palmitoleic acid (16:1n7c) (per SD) with log-transformed HOMA-IR score at baseline in Multi-Ethnic Study of Atherosclerosis participants. Absolute difference related to 1 SD increase (95% CIs) are presented; *P*-values and race-interactions are indicated where significant ($P < 0.05$). Individuals with prevalent diabetes or missing covariates were excluded.

Fatty acid	Black	Caucasian	Chinese American	Hispanic
Vaccenic acid				
Model 1	−0.18 (−0.21–−0.15)	−0.16 (−0.18–−0.14)	−0.20 (−0.23–−0.16)	−0.19 (−0.22–−0.16)
	< 0.001	**< 0.001**	**< 0.001**	**< 0.001**
Model 2	**−0.12 (−0.14 – −0.09)**	**−0.09 (−0.11 – −0.072)**[d]	**−0.10 (−0.13 – −0.063)**	**−0.11 (−0.14 – −0.085)**[b]
	< 0.001	**< 0.001**	**< 0.001**	**< 0.001**
Palmitoleic acid				
Model 1	0.08 (0.04–0.12)[bc]	0.03 (0.01 – 0.05)[ad]	−0.004 (−0.06 – 0.05)[ad]	0.07 (0.04 – 0.11)[bc]
	< 0.001	**0.004**	0.90	**< 0.001**
Model 2	**0.070 (0.038 – 0.10)**[bc]	**0.01 (−0.006 – 0.027)**[a]	**−0.026 (−0.071 – 0.019)**[ad]	**0.053 (0.022 – 0.083)**[c]
	< 0.001	**0.209**	**0.255**	**< 0.001**

Model 1: linear regression adjusted for age and sex; Black: N=1485; Caucasian: N=2373; Chinese American: N=685; Hispanic: N=1193

Model 2: model 1 + further adjustments for education, smoking status, alcohol consumption status, BMI, systolic blood pressure, hypertension medication, total cholesterol, HDL-C; Black: N=1465; Caucasian: N= 2351; Chinese American: N=681; Hispanic: N=1192

[a] Significantly different than Black participants

[b] Significantly different than Caucasian participants

[c] Significantly different than Chinese American participants

[d] Significantly different than Hispanic participants

Table IV.

Race-stratified cox regression analysis of plasma vaccenic acid (18:1n7c) and palmitoleic acid (16:1n7c) (per SD) with risk incident type II diabetes in Multi-Ethnic Study of Atherosclerosis participants over a median 9.3-year follow-up. Hazard ratios (95% CIs) are presented, and *P*-values and race-interactions are indicated where significant ($P < 0.05$). Individuals with prevalent diabetes or missing covariates were excluded.

Fatty acid	Black	Caucasian	Chinese American	Hispanic
	HR (95%CI)	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Vaccenic acid				
Model 1	0.74 (0.63 – 0.86)[c]	0.79 (0.68 – 0.92)[cd]	0.48 (0.37 – 0.63)[ab]	0.61 (0.52 – 0.72)[b]
	< 0.001	**0.003**	**< 0.001**	**< 0.001**
Model 2	**0.83 (0.71 – 0.97)[c]**	**0.95 (0.81–1.11)[cd]**	**0.61 (0.46–0.81)[ab]**	**0.68 (0.58 – 0.81)[b]**
	0.019	**0.518**	**< 0.001**	**< 0.001**
Palmitoleic acid				
Model 1	1.18 (1.00 – 1.39)	1.22 (1.08 – 1.37)	0.98 (0.70 – 1.37)	1.15 (0.99 – 1.34)
	0.05	**0.001**	0.91	0.08
Model 2	**1.21 (1.01 – 1.45)**	**1.14 (1.00 – 1.30)**	**0.98 (0.69 – 1.39)**	**1.14 (0.97 – 1.35)**
	0.037	**0.057**	**0.893**	**0.112**

Model 1: Cox regression with adjustments for age and sex (Black: N=1399, 204 cases; Caucasian: N=2295, 202 cases; Chinese American: N=640, 81 cases; Hispanic: N=1124, 178 cases)

Model 2: model 1 + adjustments for education, smoking status, alcohol consumption status, BMI, systolic blood pressure, hypertension medication, total cholesterol, HDL-C (Black: N=1380, 201 cases; Caucasian: N= 2274, 200 cases; Chinese American: N=636, 81 cases; Hispanic: N=1123, 178 cases)

[a]Significantly different than Black participants

[b]Significantly different than Caucasian participants

[c]Significantly different than Chinese American participants

[d]Significantly different than Hispanic participants