# Polyunsaturated fatty acids effect on serum triglycerides concentration in the presence of metabolic syndrome components. The Alaska-Siberia Project

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## Abstract

Serum fatty acids (FAs) have wide effects on metabolism: Serum saturated fatty acids (SFAs) increase triglyceride (TG) levels in plasma, whereas polyunsaturated fatty acids (PUFAs) reduce them. Traditionally, Eskimos have a high consumption of omega-3 fatty acids ($\omega$3 FAs); but the Westernization of their food habits has increased their dietary SFAs, partly reflected in their serum concentrations. We studied the joint effect of serum SFAs and PUFAs on circulating levels of TGs in the presence of metabolic syndrome components. We included 212 men and 240 women (age, 47.9 ± 15.7 years; body mass index [BMI], 26.9 ± 5.3) from 4 villages located in Alaska for a cross-sectional study. Generalized linear models were used to build surface responses of TG as functions of SFAs and PUFAs measured in blood samples adjusting by sex, BMI, and village. The effects of individual FAs were assessed by multiple linear regression analysis, and partial correlations ($r$) were calculated. The most important predictors for TG levels were glucose tolerance ($r = 0.116$, $P = .018$) and BMI ($r = 0.42$, $P < .001$). Triglyceride concentration showed negative associations with 20:3$\omega$6 ($r = -0.16$, $P = .001$), 20:4$\omega$6 ($r = -0.14$, $P = .005$), 20:5$\omega$3 ($r = -0.17$, $P < .001$), and 22:5$\omega$3 ($r = -0.26$, $P < .001$), and positive associations with palmitic acid ($r = 0.16$, $P < .001$) and 18:3$\omega$3 ($r = 0.15$, $P < .001$). The surface response analysis suggested that the effect of palmitic acid on TG is blunted in different degrees according to the PUFA chemical structure. The long-chain $\omega$3, even in the presence of high levels of saturated fat, was associated with lower TG levels. Eicosapentaenoic acid (20:5$\omega$3) had the strongest effect against palmitic acid on TG. The total FA showed moderate association with levels of TG, whereas SFA was positively associated and large-chain PUFA was negatively associated. The Westernized dietary habits among Eskimos are likely to change their metabolic profile and increase comorbidities related to metabolic disease.
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## 1. Introduction

The recent increase in cardiovascular disease (CVD) and type 2 diabetes mellitus (DM) among Alaska Natives may be partially related to increased life span, but it also appears to be related to the improving economy in the past 35 years. With Alaskan statehood came considerable wealth, including cash for store-bought foods, 4-wheelers, snow machines, and televisions. This has resulted in the uninformed purchase of Western foods in stores and, for many, the development of a sedentary lifestyle. Where life was once a real struggle, with extensive energy expenditures, the life for many is now more relaxed for both sexes; but women's energy expenditure has been greatly reduced, resulting in a high prevalence of obesity [1-3].

Free serum fatty acids (FFAs) have wide effects on metabolism, and their excessive intake produces insulin resistance in animals and humans [4,5]. Serum cholesterol levels increase when diet includes a high concentration of saturated fat, whereas they decrease in the presence of

polyunsaturated fatty acids (PUFAs) [6]. A meta-analysis conducted by Mensink et al [7] showed that replacement of carbohydrates by PUFAs decreased the level of triglycerides (TGs). Saturated fats (SFAs), like stearic and palmitic acids, have a marked stimulatory effect on glucose-mediated insulin secretion in perfused pancreas, a finding that has been confirmed recently [8]. Meanwhile, epidemiologic studies show a positive relationship between monounsaturated fatty acids and $\beta$-cell insulin secretion [9].

The possibility that overconsumption of certain specific fats can facilitate the development of DM has emerged only recently. The suggestion comes from 3 studies: (1) our findings of elevated plasma levels of palmitic acid in participants with impaired glucose tolerance and previously undiagnosed DM [1], (2) our intervention study aimed at decreasing consumption of palmitic acid, and (3) experiments in which adult rat pancreatic islets were cultured on plates [1]. These cultured plates showed a clear lipotoxic effect of palmitic acid by increased apoptosis rate coupled with reduced proliferation capacity of $\beta$-cells and, consequently, impaired insulin secretion. The deleterious effect of palmitate on $\beta$-cell turnover is mediated via formation of ceramide and activation of the apoptotic mitochondrial pathway.

Relatives of individuals with DM have increased FFAs availability that contribute to mitochondrial dysfunction, which can be the initial step to develop other abnormalities such as accumulation of intramyocellular lipids, impaired lipid oxidation, and insulin resistance [10].

Guidelines from the American Heart Association for weight management emphasizes limiting consumption of saturated fat to less than 10% of total energy intake and considering the beneficial effects of $\omega 3$ FA supplements [11]. There are limited studies related to the association of total and relative concentration of specific FAs in relation to the total pool of TGs and how this is affected by glucose, high-density lipoprotein cholesterol (HDL-C), blood pressure, and waist circumference.

To address if the $\omega 3$ concentration affects the metabolic syndrome (MetS) components, we can approach the problem analyzing each MetS component. This approach is incomplete because it does not consider the MetS as a whole cluster where each component is conditioned by the presence of others; the clusters are due to the common base of insulin resistance [12]. Each MetS component is not independent from the others. Even more, their dependence is not equal for each combination of MetS components. Some combinations have higher likelihood to be dependent than others, so we considered that the best approach was to include the whole cluster [13].

The canonical regression was used as a multivariate approach that considered all MetS components at the same time with respect to their relation with total FAs. We described how the absolute plasma concentration (in milligrams per milliliter) and relative concentration (percentage in the red cell membrane) of specific FAs correlate with serum TGs in the presence of MetS components.

## 2. Materials and methods

### 2.1. Study population

We invited 212 men and 240 women between 25 and 91 years of age from 4 villages (1 Inupiat, 1 Central Yupik, and 2 Siberian Yupik villages) in the Norton Sound Region of Alaska to participate in the study. The overall response from the potential sample population was 50% men and 67% women. All subjects were screened during a 4-week period in 1994.

### 2.2. Study screening

This project followed the Strong Heart Study Protocol [14] that consisted of a personal interview (including medical history), physical examination (including blood pressure measurements and electrocardiogram), blood sampling, and nutritional interviews using 24-hour recall and food frequency instruments [1,15]. The latter were conducted the day before the blood sampling. Blood chemistries were carried out at the Medstar Research Institute that also does the analysis for the Strong Heart Study. The methods used have been described elsewhere [14]. Insulin was measured using a radioimmunoassay developed as a modification of the method of Morgan and Lazarow as referenced by Lee et al [14].

Anthropometric measurements included hip circumference, height, weight, and waist (at umbilicus) circumference [15,16]. After the participant had rested for 5 minutes in the sitting position, 3 consecutive blood pressure measurements were made on the right arm with a standard stethoscope, an appropriate-sized cuff, and a Baum mercury sphygmomanometer (WA Baum, Copiaque, NY), using the first- and fifth-phase Korotkoff sounds. The mean of the last 2 measurements was used to estimate the blood pressure.

### 2.3. Plasma FA analysis

Plasma FAs were analyzed at the University of Alaska Anchorage [1] in 1994 and has been described elsewhere [1,15]. The concentration of each FA was determined for each sample using regression analysis. The ratio of the area of each FA peak to the internal standard peak was plotted against the weight ratio of the FA and the internal standard. The regression equation was used to calculate the concentration of each FA in each sample. Typical correlations were 0.99 or better.

Finally, we studied the $\Delta^6$ desaturation index, a known measurement associated with CVD [17]:

$$\Delta 6 - \text{desaturation} = \frac{18:3\omega 6 + 20:3\omega 6}{18:2\omega 6}$$

### 2.4. Statistics

General descriptions of variables are shown as mean ± standard deviation. Canonical correlation was conducted

with 397 subjects (204 men and 193 women) that completed the matrix of all MetS components. Sex is related to important metabolic differences; therefore, each sex was analyzed separately. We used the first canonical variate to calculate the correlation between every 2 sets of variables [18]. The canonical structure matrix was calculated using the canonical variate scores with the original data. The $P$ value was calculated according to the method described by Bartlett [19].

Waist circumference is a MetS component, but it explains partially the presence of other MetS components. This inconsistency led us to run models with waist circumference at the explanatory side of the canonical equation and to run another model with waist circumference at the explained side. These sides (explanatory or explained) are simple conventions according to the subjacent biological background of the hypothesis.

The models included body mass index (BMI) and waist circumference, but they were analyzed separately because of their high correlation (colinearity $r = 0.9$, $P < .01$).

Multiple linear regression was used to adjust for variables that explain serum TG variation. Sex, age, village, waist circumference, and BMI were used as adjustment variables. We worked with first-order interaction models to maintain a simple way to understand basic relationships.

We tested the hypothesis that increasing weight and serum glucose should be positively associated with higher desaturation index, and the stepwise backward method was used to define the model. We considered a $P$ value <.10 as an important contributor of the TG variation. Each model was assessed by residual analysis of Cook, Mahalanobis, and leverage distances. Surface response graphics were built to show the interaction results obtained from the multiple linear model.

## 3. Results

We analyzed 212 men and 240 women (age, $47.9 \pm 15.7$ years; BMI, $26.9 \pm 5.3$) from 4 villages located in Alaska.

The analysis showed important sex differences for anthropometric measurements and insulin resistance markers but not for serum FA levels (Table 1). It is remarkable that this population has, on the average, high fasting glucose levels but low homeostasis model assessment of insulin resistance (HOMA-IR) index, low serum TGs, and high HDL-C.

### 3.1. Clusters of MetS

The canonical correlations variates showed the relation between the MetS components and the studied serum lipids.

Serum FAs (described in Table 2) were related mainly to TGs and diastolic blood pressure in women (Rc = 0.71, $P < .0001$) and men (Rc = 0.67, $P < .0001$). The association was significant for systolic blood pressure, waist circumference,

Table 1

Comparison between sexes for anthropometric measurements, blood pressure, lipid profile, and insulin resistance

| Variable | Women | Men | $P$ value |
|---|---|---|---|
| Age (y) | $48.3 \pm 16$ | $46.1 \pm 15$ | .165 |
| Waist circumference (cm) | $93.0 \pm 15$ | $89.7 \pm 12$ | .013 |
| BMI | $27.3 \pm 5.5$ | $25.9 \pm 4.2$ | .003 |
| Systolic BP (mm Hg) | $117 \pm 19$ | $118 \pm 14$ | .902 |
| Diastolic BP (mm Hg) | $72.5 \pm 12$ | $75.6 \pm 11$ | .009 |
| Cholesterol (mg/dL) | $227.3 \pm 40$ | $225.4 \pm 47$ | .676 |
| TGs (mg/dL) | $75.3 \pm 54$ | $74.5 \pm 53$ | .879 |
| HDL-C (mg/dL) | $60.6 \pm 16.7$ | $54.1 \pm 15.9$ | <.001 |
| Fasting glucose (mg/dL) | $100.1 \pm 12$ | $101 \pm 11$ | .332 |
| HOMA-IR | $1.8 \pm 1.2$ | $1.5 \pm 1.0$ | .002 |
| Insulin ($\mu$U/L) | $7.3 \pm 4.4$ | $5.8 \pm 3.7$ | <.001 |

Serum FAs are not shown because they had no significant differences between sexes. Comparisons were made by Student $t$ test adjusted for variance. Data are expressed as mean $\pm$ SD. BP indicates blood pressure.

and glucose only in men. The structural coefficient shows that the contribution of TGs to the canonical variates was the highest of all metabolic components for both sexes ($r = 0.904$ for women and $r = 0.905$ for men). The results can be seen in Table 2.

The most important FA association with the cardiovascular risk variables in women and men were 18:1$\omega$9 ($r = 0.291$, $r = 0.375$), 18:2$\omega$6 ($r = 0.124$, $r = 0.187$), 18:3$\omega$3 ($r = 0.122$, $r = 0.213$), 18:3$\omega$6 ($r = 0.194$, $r = 0.297$), 20:3$\omega$6 ($r = 0.179$, $r = 0.176$), and 20:5$\omega$3 ($r = -0.304$, $r = -0.245$; all with $P < .05$, respectively) (Table 2). Interestingly, women showed a slight additional effect of 20:4$\omega$6 ($r = -0.01$, $P = .011$); and men, of 18:0 ($r = 0.107$, $P = .057$). The waist circumference was a very important variable that correlated with the canonical variate $r = 0.71$ for women and $r = 0.54$ for men ($P < .001$ for both).

In a previous exploratory model, we tested the waist circumference at the dependent side of the equation ("Statistics"). The contribution of TG to the canonical variate remained important.

### 3.2. Levels of serum TGs associated with FA concentration

Based on our canonical model, we decided to analyze the effect of FAs on TG variation using multiple linear regression models. The initial model included serum FA and its interactions, adjusted by age, sex, waist circumference, BMI, and HOMA index. Two models were tested: (1) absolute serum levels of FA and (2) relative proportion (percentage) of serum FA. The model with absolute concentration of FA showed multiplicative interaction between 20:5$\omega$3 and 16:0, 18:1$\omega$9 and 18:2$\omega$6, 18:1$\omega$9 and 18:3$\omega$6, 18:2$\omega$6 and 20:3$\omega$6, and 18:3$\omega$3 and 20:3$\omega$6 (Table 3).

The adjusted serum TGs and the interaction between FAs as percentage and as absolute serum levels can be seen in Figs. 1 and 2, respectively. The described associations remained despite adjustment using HOMA-IR as covariate.

Table 2
Canonical loadings and matrix structure

| MetS component | Women (n = 204) | | | Men (n = 193) | | |
|---|---|---|---|---|---|---|
| | Loading | P value | Structure coefficients | Loading | P value | Structure coefficients |
| Explained variables | | | | | | |
| Systolic BP | 1.247 | .009 | 0.133 | −0.995 | .125 | 0.157 |
| Diastolic BP | −0.267 | .507 | 0.495 | 2.009 | <.001 | 0.433 |
| HDL-C | −0.390 | .096 | −0.577 | −0.523 | .015 | −0.607 |
| TGs | 1.696 | <.001 | 0.904 | 1.509 | <.001 | 0.915 |
| Glucose | 0.407 | .770 | 0.021 | −0.155 | .750 | 0.003 |
| Total cholesterol | −1.168 | .001 | −0.016 | −1.481 | <.001 | −0.083 |
| Explicative variables | | | | | | |
| 16:0 | 0.537 | .183 | 0.218 | 0.119 | .738 | 0.333 |
| 18:0 | 0.782 | .177 | 0.019 | −0.837 | .057 | 0.107 |
| 18:1$\omega$9 | 2.207 | <.001 | 0.291 | 1.652 | <.001 | 0.375 |
| 18:2$\omega$6 | −1.863 | <.001 | 0.124 | −0.533 | .002 | 0.187 |
| 18:3$\omega$3 | 2.143 | <.001 | 0.122 | 1.009 | .047 | 0.213 |
| 18:3$\omega$6 | 2.094 | .006 | 0.194 | 3.319 | <.001 | 0.297 |
| 20:3$\omega$6 | −1.574 | .004 | 0.179 | −1.683 | .003 | 0.176 |
| 20:4$\omega$6 | −0.896 | .011 | −0.008 | −0.362 | .259 | −0.053 |
| 20:5$\omega$3 | −1.106 | <.001 | −0.304 | −0.749 | <.001 | −0.249 |
| 22:6$\omega$3 | 0.197 | .629 | −0.119 | −0.014 | .948 | −0.135 |
| Age (y) | −0.033 | .885 | −0.239 | −0.966 | <.001 | −0.291 |
| Waist | 2.626 | <.001 | 0.707 | 4.417 | <.001 | 0.542 |

The matrix structure was calculated with the correlation of the canonical variates against the original variables. The first canonical correlation root was 0.77 (P < .001) for women and 0.78 (P < .001) for men.

The $\Delta^6$ desaturation index did not explain the variation of TGs; most of its variation was associated with serum insulin levels ($r = 0.32$, $P < .001$), BMI ($r = 0.19$, $P < .0001$), and waist circumference ($r = 0.25$, $P < .001$) (the last 2 were analyzed in separate models).

## 4. Discussion

This study demonstrates that the interaction between different types of FAs is associated mainly with serum TGs compared with other studied variables related to insulin

Table 3
Multiple linear regression for serum TG concentration

| Variable | Stand $\beta$ | Partial $r$ | P value | Stand $\beta$ | Partial $r$ | P value |
|---|---|---|---|---|---|---|
| Age (y) | −0.062 | −0.082 | .096 | −0.075 | −0.097 | .049 |
| Waist (cm) | 0.170 | 0.208 | <.001 | 0.225 | 0.257 | <.001 |
| HOMA index | 0.218 | 0.270 | <.001 | 0.229 | 0.267 | <.001 |
| 16:0 | −1.055 | −0.164 | .001 | 0.526 | 0.291 | <0.001 |
| 18:1$\omega$9 | | | | 0.611 | 0.457 | <.001 |
| 18:2$\omega$6 | −3.738 | −0.325 | <.001 | | | |
| 18:3$\omega$3 | | | | 0.563 | 0.335 | <0.001 |
| 18:3$\omega$6 | 1.086 | 0.254 | <.001 | 0.386 | 0.193 | <.001 |
| 20:3$\omega$6 | −2.251 | −0.265 | <.001 | | | |
| 20:4$\omega$6 | −0.170 | −0.120 | .015 | 0.329 | 0.100 | .041 |
| 20:5$\omega$3 | −2.851 | −0.224 | <.001 | −0.109 | −0.107 | .030 |
| 22:5$\omega$3 | | | | −0.138 | −0.103 | .035 |
| 22:6$\omega$3 | | | | 0.089 | 0.104 | .035 |
| 20:3$\omega$6 * 16:0 | | | | −0.244 | −0.154 | .002 |
| 20:4$\omega$6 * 16:0 | | | | −0.382 | −0.136 | .006 |
| 20:5$\omega$3 * 16:0 | 3.078 | 0.199 | <.001 | | | |
| 18:1$\omega$9 * 18:2$\omega$6 | 3.110 | 0.271 | <.001 | | | |
| 18:1$\omega$9 * 18:3$\omega$6 | −0.971 | −0.155 | .002 | | | |
| 18:2$\omega$6 * 20:3$\omega$6 | 1.800 | 0.178 | <.001 | | | |
| 18:3$\omega$3 * 20:3$\omega$6 | 0.75 | 0.221 | <.001 | | | |

The first 3 columns are for FA in absolute serum concentration values (in milligrams per milliliter), and the other 3 columns are for FA measured as relative concentrations (percentage). Blank spaces denote nonsignificant effect. Stand indicates standardized coefficients.
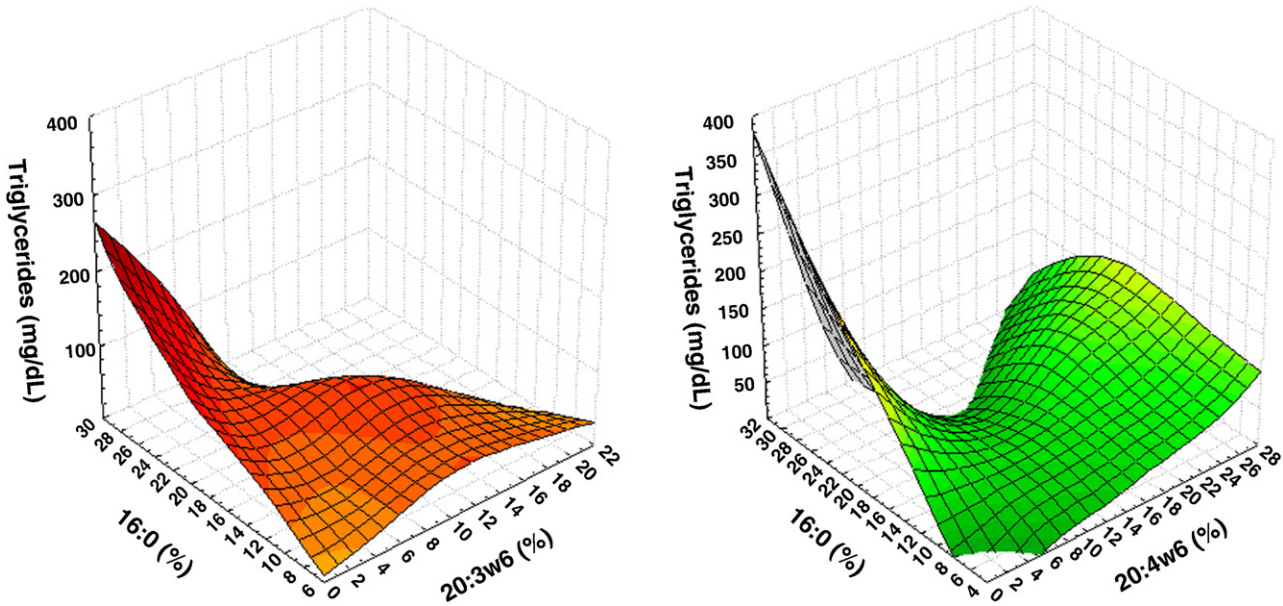
Fig. 1. Serum TG concentration is affected by the interaction of relative concentrations of FAs. Figures show positive association of serum TGs with palmitic acid only in the presence of low relative concentration of $20:3\omega6$ and $20:4\omega6$. This association is blunted in the presence of higher concentration of this $\omega6$.

resistance. This relationship was independent of the HOMA-IR measurement and differs according to whether the FAs are considered as absolute serum concentration or relative (percentage) component. The absolute variation of PUFAs showed an important inverse correlation with TGs and other components of MetS. Cholesterol concentration was not affected by such variation.

The current criteria for MetS include the waist circumference; but this is a causal factor for the other 4 components, yielding to controversial aspects about its clinical utility [20].

We considered that the best way to understand our model with biological basis was to include the waist circumference in the explanatory side of the canonical correlation. The effect of $\omega3$ FA upon TGs remained significant despite the waist circumference at the explained side of the equation, which supports the independent association of $\omega3$ FA with TG concentration.

We included in the explained side of the canonical equation the total cholesterol as another metabolic component associated with coronary disease, but it is clear that TG
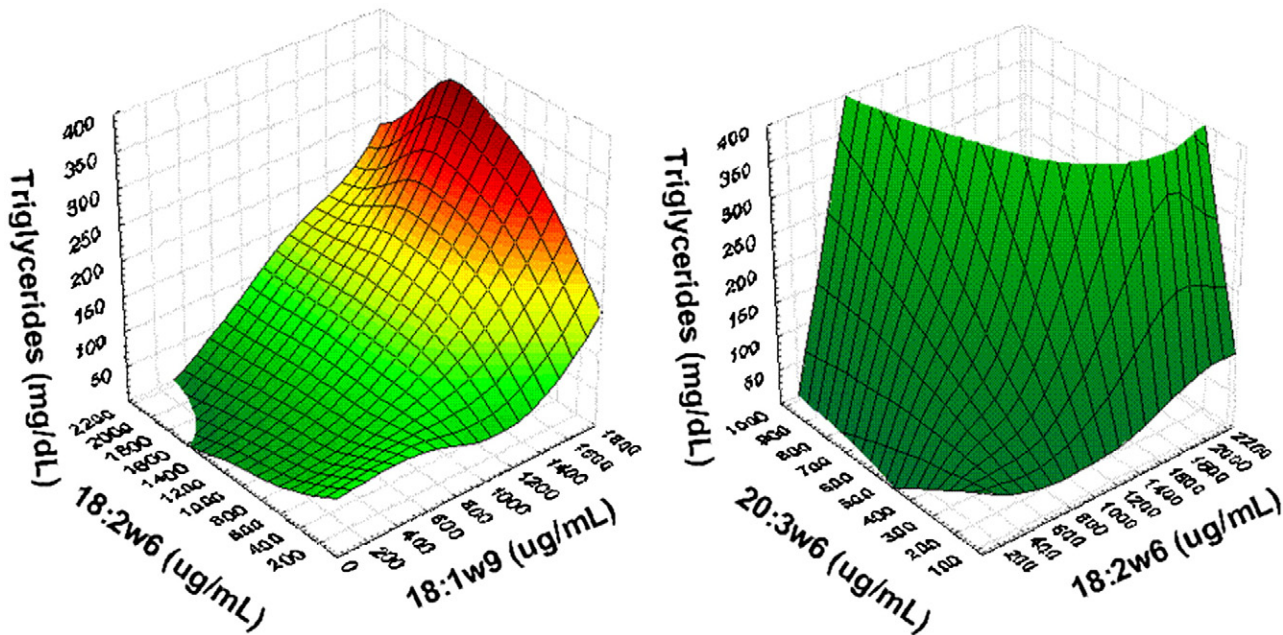


Fig. 2. Serum TGs are positively associated with the interaction of absolute concentration of $18:1\omega9$, $18:2\omega6$, and $20:3\omega6$. The absolute concentration of FAs is closely related with the TG concentration.

concentration remained associated with the specific $\omega$3 FA concentration.

It is clear that each FA has its own particular effect on metabolism. Intervention studies have shown that FA composition of structured triacylglycerols affects its digestion and absorption; moreover, the inclusion of some monounsaturated fat can prevent fat accumulation in healthy individuals [21].

The studied population showed high average serum glucose levels; but these were accompanied by low HOMA-IR index and, most remarkably, the presence of low levels of TGs and high HDL-C. This unique metabolic profile may be related to environmental or genetic differences, which influence specific phenotypes; that is, it is known that adipose tissue depot in muscle (metabolic effect) is influenced by ethnicity (environment and genetic effects) [22].

The study of whether the recently introduced nontraditional foods are harmful to these populations has only recently begun [15]. The plasma content of C20 and C22 $\omega$3 FAs is derived from fish and marine mammals, principal components of traditional Eskimo diet [1]. Lack of information about healthy food has resulted in many Eskimos turning from healthy traditional foods, rich in $\omega$3 FAs and low in saturated fats, to store-bought foods high in saturated and *trans* FAs. Young Eskimos currently consume large amounts of nontraditional fat [1]. Thus, ethnic-specific craving for such items as Eskimo ice cream (now made from shortening and berries) has led to a distinct change in fat consumption. The frequently purchased items high in 16:0 and *trans* 18:1-9 FAs are butter, shortening, margarine, and bacon. Our screening of 454 Alaskan Eskimos revealed that many exceeded the fat and saturated fat restrictions consistent with the Step 1 National Cholesterol Education Program recommendations: 42% of individuals had diets that had at least 10% saturated fat, 61.1% had diets that had at least 300 mg cholesterol, and 81% had diets that had at least 30% total fat.

Considering that DM and CVD were rare in this population only 40 years ago on a traditional diet, it is easy to imagine that change in fat consumption in this population contributes to disease. It is also likely, but not yet proven, that other Native Americans have changed their fat consumption. For example, the Pima Indians now also use Crisco shortening in considerable quantities in tortillas and fried bread.

A challenge in clinical trials for testing diets is the low adherence to the diet; however, the data consistently show that fish diet and fish oil reduce the overall risk of coronary death [23].

The levels of FAs are not only related to diet consumption, but also to the expression of enzyme activity that can contribute to the phenotypes of MetS. The activity of the 11-b-hydroxysteroid dehydrogenase type 1 in adipose tissue has been associated with fasting glucose, insulin levels, and insulin resistance [24,25]. However, the clinical significance is still controversial because the enzyme can be a marker and not a determinant of obesity and insulin resistance [26].

### 4.1. Study limitations

This cross-sectional design does not reveal the possible mechanisms that explain the causality of the model. Temporality cannot be tested. However, the intervariable correlational analysis conducted here can help understand the relationship between variables.

### 4.2. Study strengths

Direct serum measurement of different types of FAs can help understand how their serum concentration is related to variables related to CVD. The analysis of complex traits is difficult because many variables act together at the same time. Analyses by multivariate methods become a key to understand the complex association between variables.

We considered the interaction between FAs. This first-order interaction helps understand the relation ship between percentages compared with absolute values. These 2 analyses showed different relationship between FAs and TGs, suggesting different metabolic pathways for plasma FAs and FA percentage within red cell membranes. In other words, these measurements of FAs concentration are not equivalent and are phenotypes of complex subjacent metabolism and not the simple fat ingestion.

## 5. Conclusions

The amounts of absolute plasma concentration or relative concentration of specific FAs are related to TG concentration. The FAs can play a causal role for subsequent complications of MetS, and the metabolic effect is related with the biochemical configuration associated with different metabolic pathways for each FA. The controversy remains; however, the waist circumference looks better as an explanatory variable, independent of the $\omega$3 concentration, of the TG concentrations and the other 4 MetS.

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