Original Contribution

Serum Omega-6 Polyunsaturated Fatty Acids and the Metabolic Syndrome: A Longitudinal Population-based Cohort Study

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Initially submitted August 1, 2011; accepted for publication December 13, 2011.

The serum fatty acid composition reflects the dietary fatty acid composition from the past few days to several weeks. However, the role of serum omega-3 (from fish and fish oils) and omega-6 (from vegetable oils) polyunsaturated fatty acids (PUFAs) in the course of metabolic syndrome is poorly understood. At the Primary Health Care Unit in Piekämäki, Finland, all subjects born in 1942, 1947, 1952, 1957, and 1962 (n = 1,294) were invited for health checkups in 1997–1998 and 2003–2004. Metabolic syndrome was defined by using the new, harmonized criteria. The serum omega-3 PUFAs, omega-6 PUFAs, and total fatty acids were analyzed by proton nuclear magnetic resonance spectroscopy. Altogether, data from both checkups were available for 665 subjects. After adjustment for age, sex, and baseline body mass index, the incidence of metabolic syndrome between the 2 checkups with a 6.4-year follow-up was inversely associated (P < 0.001) with the increased relative proportion of omega-6 PUFAs in serum lipids. Further adjustment for body mass index change, lipid medication, smoking, alcohol intake, and physical activity conveyed similar results. The authors did not find any significant associations between omega-3 PUFAs and the incidence of metabolic syndrome. Therefore, their results suggest that the change in the relative proportion of omega-6 PUFAs in serum lipids is inversely related to the incidence of metabolic syndrome.

cohort studies; fatty acids, omega-3; fatty acids, omega-6; Finland; metabolic syndrome X; polyunsaturated fatty acids

Abbreviations: CI, confidence interval; HDL, high density lipoprotein; PUFA, polyunsaturated fatty acid.

Metabolic syndrome includes a constellation of cardiovascular and type 2 diabetes risk factors (1). The etiology of metabolic syndrome involves complex interactions among genetic, metabolic, and environmental factors, including diet (2–4). Because of the worldwide obesity epidemic, metabolic syndrome represents the increasing health problems that are seen in primary health-care settings (5).

The role of diet, especially dietary polyunsaturated fatty acids (PUFAs), in the etiology and development of metabolic syndrome is poorly understood (6, 7). Fish and fish oil-derived omega-3 PUFA supplementation may decrease insulin resistance, triglyceride levels, and blood pressure and may remediate the effects of metabolic syndrome (8). Vegetable oil-derived omega-6 PUFAs may compete with omega-3 PUFAs in several physiologic processes and are abundant in the Western diet (9, 10). Moreover, omega-6 PUFAs may increase inflammatory signals and have been linked to cardiovascular diseases (11). Population-based intervention studies have revealed contradictory results (12, 13), although some evidence suggests that an increase in the omega-3:omega-6 PUFA ratio might be effective in reducing insulin resistance and the prevalence of metabolic syndrome (14). Other studies have suggested that there is no link between different dietary intakes of omega-3 PUFAs and omega-6 PUFAs and the prevalence of metabolic syndrome (15). However, only a few longitudinal, population-based studies have been conducted to examine serum PUFAs and their role in the development of
metabolic syndrome. The present study used a population-based cohort with 6.4 years of follow-up to investigate the role of serum omega-3 and omega-6 PUFAs in the incidence of metabolic syndrome.

MATERIALS AND METHODS

Study population

All of the residents of Pieksämäki, Finland, who were born in 1942, 1947, 1952, 1957, and 1962 (n = 1,294) were invited for a health checkup in 1997–1998 (baseline visit) and again in 2003–2004. Of those invited, 923 (71%) participated in the first checkup, and 681 subjects (74%) attended both checkups. Of those 681 subjects, 665 yielded all of the data needed for the analysis of the study. The protocol was approved by the Kuopio University Hospital Ethics Committee. All participants gave written informed consent.

Clinical and laboratory procedures

Health evaluations were performed by the same 2 nurses at both checkups. Sitting blood pressure was measured with a mercury sphygmomanometer after 15 minutes of rest. The measurement was repeated 5 minutes later, and the mean of the 2 measurements was used in the statistical analyses. Waist circumference was measured from the midpoint between the lateral iliac crest and the lowest rib to the nearest 0.5 cm. Weight and height were measured to the nearest 0.1 kg and 0.5 cm, respectively. Body mass index was calculated as weight (kg)/height (m) squared.

Blood samples were taken after an overnight fast. The plasma glucose concentration was measured by using an automated colorimetric method (Peridochrom Glucose GOD-PAP; Boehringer Mannheim GmbH, Mannheim, Germany). Serum triglycerides and cholesterol were measured from fresh serum samples by using, respectively, GPO-PAP and CHOD-PAP enzymatic colorimetric methods (Boehringer Mannheim GmbH). Serum high density lipoprotein (HDL) cholesterol was measured by using the same method (CHOD-PAP) after the precipitation of apolipoprotein B-containing lipoprotein particles by phosphotungstic acid and magnesium. The serum was separated by centrifugation for the determination of the fatty acids, immediately frozen at −70°C, and slowly thawed in a refrigerator at 4°C overnight before sample preparation. Lipids were extracted from the serum samples by using a standard protocol; lipoprotein particles were broken down with methanol and dichloromethane. Proton nuclear magnetic resonance spectroscopy was used for the determination of serum lipid constituents and the diversity of fatty acid saturation in the extract samples as previously described (16, 17). Briefly, the data were recorded by using a high-throughput platform with the Bruker AVANCE III spectrometer (Bruker BioSpin Corporation, Billerica, Massachusetts) operating at 500.36 MHz. A standard pulse sequence was used to acquire the data. Individual serum lipid constituents were quantified and calibrated as mmol/L by using the total cholesterol concentration in native serum as the reference (16, 17). The omega-3 and omega-6 PUFAs and the sum of the omega-7, omega-9, and saturated fatty acids were determined. For statistical analysis, ratios of different fatty acid concentrations (mmol/L) to the total fatty acid concentration (mmol/L) were calculated and expressed as mmol/100 mmol.

At the beginning and at the end of the research period, metabolic syndrome was defined according to the new, harmonized criteria (18). Subjects with 3 or more of the following components were classified as having metabolic syndrome: 1) increased waist circumference, that is, the waist criterion (≥102 cm for men and ≥88 cm for women); 2) elevated fasting total triglycerides, that is, the triglyceride criterion (≥1.7 mmol/L or treatment for dyslipidemia); 3) low fasting serum HDL cholesterol, that is, the HDL criterion (<1.03 mmol/L for men and <1.29 mmol/L for women or treatment for dyslipidemia); 4) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or the use of antihypertensive medication, that is, the blood pressure criterion; and 5) fasting plasma glucose of ≥5.6 mmol/L or the use of medication for hyperglycemia, that is, the glucose criterion (19).

Brief intervention procedure

All of the subjects completed a questionnaire that included questions about their medication, smoking habits, alcohol consumption, physical activity, and consumption of hard fats in food. During the health examination, the nurses were guided to counsel all participants to lead more healthy lifestyles, including advice for weight loss, smoking cessation, increasing exercise, and abstaining from alcohol, exchanging hard fats for smooth fats and liquid margarines, using olive or rapeseed oils, in the preparation of food and increasing fish consumption. All subjects were also given problem-specific informational leaflets corresponding to their recorded health problem.

Statistical analyses

The data are presented as the means and standard deviations or as counts with percentages. The 95% confidence intervals for the most important outcomes were obtained by bias-corrected bootstrapping (5,000 replications). The statistical comparisons between groups were performed by using the t test or the bootstrap-type t test, the chi-square test, or Fisher’s exact test when appropriate. The linearity across the 4 metabolic syndrome groups was tested by using bootstrap-type general linear models with the appropriate contrast. Age, body mass index, change in body mass index, smoking status, physical activity, and the use of alcohol were added to the model as covariates. All P values reported are 2 sided.

RESULTS

All of the required variables at both checkups were available from 665 subjects (274 men and 391 women). At baseline, metabolic syndrome was present in 31% of the subjects (92 men and 111 women), and these subjects were

removed from the final follow-up study population; after this exclusion, the study population included 462 subjects (182 men and 280 women). During the follow-up time, metabolic syndrome had developed in 26% (49 men and 68 women) of the cohort. We observed no statistically significant differences in baseline alcohol consumption, education, physical activity, or marital status between the genders or between the subjects who did or did not have the metabolic syndrome at follow-up.

More of the 258 subjects of the 923 participants studied in 1996–1997 that did not participate in the second health checkup in 2003–2004 lived alone (30% of the nonparticipants vs. 21% of the participants; \( P = 0.045 \)), smoked (45% vs. 28%; \( P < 0.001 \)), and used on average at least 2 units/day of alcohol (13% vs. 6%; \( P = 0.003 \)). Biochemical measurements, prevalence of the metabolic syndrome, and use of medication for hypertension, diabetes, and dyslipidemia were similar in both groups.

The mmol/100 mmol of omega-3 PUFA was positively correlated after adjustments for age, sex, and body mass index with HDL cholesterol \( (r = 0.115; P = 0.003) \) but not with triglycerides. The mmol/100 mmol of omega-6 PUFA was positively correlated with HDL cholesterol \( (r = 0.21; P < 0.001) \) and negatively correlated with the triglyceride concentration \( (r = −0.57; P < 0.001) \). We observed no other statistically significant correlations between the mmol/100 mmol of omega-3 PUFA or omega-6 PUFA and the total cholesterol, waist circumference, systolic/diastolic blood pressure, or fasting blood glucose concentrations at baseline. Similar results were found when we analyzed these correlations using the cross-sectional data of the second health checkup and, in addition to the findings at baseline, we found a statistically significant association between the mmol/100 mmol of omega-6 PUFA and the fasting glucose level \( (r = −0.193; P < 0.001) \).

In both sexes, the absolute concentration of omega-3 PUFA as mmol/L was statistically higher \( (P < 0.001) \), but the mmol/100 mmol of omega-3 PUFA was similar in subjects with metabolic syndrome compared with the subjects without metabolic syndrome. The absolute omega-6 PUFA concentration was similar, but the mmol/100 mmol of omega-6 PUFA was significantly lower \( (P < 0.001) \) among subjects with metabolic syndrome compared with subjects without metabolic syndrome (Table 1). The results were similar when we used the cross-sectional data of the second health checkup in the analysis (data not shown).

Figure 1 presents the age- and sex-adjusted mean ratios of omega-3 PUFA mmol/100 mmol, omega-6 PUFA mmol/100 mmol, and the omega-3:omega-6 PUFA ratio at baseline by the individual metabolic syndrome criteria and the metabolic syndrome diagnosis. The blood pressure criterion was not associated with the examined PUFAs. Low HDL cholesterol (a positive HDL criterion) was associated with both lower omega-3 and omega-6 PUFA mmol/100 mmol, but the other criteria (excluding the blood pressure criterion) and metabolic syndrome were associated with only omega-6 PUFA mmol/100 mmol.

The mean change in body mass index between the 2 checkups was 0.71 (95% confidence interval (CI): 0.53, 0.89) kg/m². The total fatty acid concentration was similar at both time points (11.3 mmol/L vs. 11.1 mmol/L; \( P = 0.184 \)). The relative proportion of omega-3 PUFA increased by 0.24 (95% CI: 0.11, 0.39; \( P < 0.001 \)) mmol/100 mmol during the follow-up from 3.64 (standard deviation, 0.94) mmol/100 mmol, and omega-6 decreased by −0.1 (95% CI: −0.5, 0.3) mmol/100 mmol from 35.1 (standard deviation, 3.6) mmol/100 mmol. The change in the omega-3 mmol/100 mmol was not correlated longitudinally with change in any of the components of the metabolic syndrome, but the change in omega-6 mmol/100 mmol was correlated \( (P < 0.001) \) with changes in lipid parameters (Table 2).

Among those who developed metabolic syndrome during the follow-up period, the unadjusted increase in the omega-3 mmol/100 mmol was 0.17 (95% CI: −0.08, 0.42) units compared with 0.26 (95% CI: 0.12, 0.40) units among those who did not develop metabolic syndrome. After adjustment for age, sex, baseline body mass index, body mass index change during the follow-up, smoking, physical activity, alcohol consumption, and lipid medication, the respective values were 0.25 (95% CI: −0.03, 0.52) units and 0.24 (95% CI: 0.09, 0.39) units. The corresponding unadjusted values for omega-6 in those who did and did not develop metabolic syndrome during the follow-up time were −1.71 (95% CI: −2.57, −0.84) mmol/100 mmol and 0.37 (95% CI: −0.06, 0.80) mmol/100 mmol and, in the fully adjusted model, they were −2.08 (95% CI: −2.94, −1.22) mmol/100 mmol and 0.46 (95% CI: −0.01, 0.92) mmol/100 mmol, respectively. Figure 2 presents the age-, sex-, and baseline body mass index-adjusted associations between changes in the omega-3 and omega-6 mmol/100 mmol and the incidence of metabolic syndrome and its individual criteria. A change in the mmol/100 mmol of omega-3 PUFA was not associated with any individual metabolic syndrome criterion or with the incidence of metabolic syndrome. The decreased omega-6 PUFA mmol/100 mmol was related to higher incidences of future waist, glucose, HDL cholesterol, and triglyceride criteria, and the incidence of metabolic syndrome was linearly correlated \( (P < 0.001) \) with the decreased omega-6 PUFA mmol/100 mmol.

**DISCUSSION**

Serum fatty acid concentrations reflect the dietary lipid composition from the past few days to several weeks (20). This population-based, longitudinal study suggests that a decrease in the relative concentration of serum omega-6 PUFAs is strongly associated with the incidence of metabolic syndrome and its individual criteria, even after taking into account age, sex, baseline body mass index, body mass index change, lipid medication, physical exercise, smoking, and alcohol consumption. A change in the body mass index has been presented as the key modulator for development of the National Cholesterol Education Program Expert Panel criteria for metabolic syndrome (21–23), but our study suggests that a relative increase in dietary omega-6 PUFAs may also have a significant role in the prevention of metabolic syndrome.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metabolic Syndrome Negative (n = 182)</td>
<td>Metabolic Syndrome Positive (n = 92)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>45.4 (5.8)</td>
<td>47.6 (6.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Body mass indexb</td>
<td>25.1 (2.4)</td>
<td>29.9 (3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>90 (7)</td>
<td>103 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134 (15)</td>
<td>145 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81 (9)</td>
<td>88 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting serum cholesterol, mmol/L</td>
<td>5.7 (0.5)</td>
<td>5.8 (1.1)</td>
<td>0.374</td>
</tr>
<tr>
<td>Fasting serum HDL cholesterol, mmol/L</td>
<td>1.39 (0.28)</td>
<td>1.16 (0.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting serum triglycerides, mmol/L</td>
<td>1.27 (0.53)</td>
<td>2.18 (1.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.77 (0.55)</td>
<td>6.33 (1.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total fatty acids, mmol/L</td>
<td>10.9 (2.2)</td>
<td>12.8 (2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Omega-3 PUFA, mmol/L</td>
<td>0.38 (0.14)</td>
<td>0.46 (0.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Omega-3 PUFA, mmol/100 mmol</td>
<td>3.6 (1.0)</td>
<td>3.7 (1.3)</td>
<td>0.176</td>
</tr>
<tr>
<td>Omega-6 PUFA, mmol/L</td>
<td>3.8 (0.4)</td>
<td>3.9 (0.7)</td>
<td>0.109</td>
</tr>
<tr>
<td>Omega-6 PUFA, mmol/100 mmol</td>
<td>34.8 (3.6)</td>
<td>31.0 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Omega-3 PUFA:omega-6 PUFA ratio</td>
<td>10.4 (5.8)</td>
<td>12.3 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker daily</td>
<td>29</td>
<td>26</td>
<td>0.583</td>
</tr>
<tr>
<td>Alcohol, ≥2 units/day</td>
<td>4</td>
<td>5</td>
<td>0.398</td>
</tr>
<tr>
<td>Physically activee</td>
<td>34</td>
<td>26</td>
<td>0.200</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high density lipoprotein; NCEP, National Cholesterol Education Program; PUFA, polyunsaturated fatty acid; SD, standard deviation.

* P < 0.05; ** P < 0.01; *** P < 0.001.

a P values between genders according to NCEP Expert Panel metabolic syndrome status.
b Body mass index: weight (kg)/height (m)^2.
c Metabolic syndrome negative in women versus metabolic syndrome negative in men.
d Metabolic syndrome positive in women versus metabolic syndrome positive in men.
e Three or more episodes of physical exercise per week.
The majority of triglyceride molecules, consisting of a glycerol backbone with 3 fatty acids, are carried in the very-low-density lipoprotein particles in the circulation. Approximately one-fourth of the total circulating fatty acids are carried in the very-low-density lipoprotein fraction. Depending on the lipoprotein lipase activity and the dietary fat intake, the total concentration of triglycerides and the concentration of fatty acids in the lipoprotein particles vary, but the composition of fatty acids is expected to remain constant. Additionally, the correlation between serum triglycerides and omega-6 PUFA mmol/100 mmol was determined in the present study.

Phospholipid molecules with 2 fatty acids attached are also major carriers of fatty acids in lipoprotein particles.

Figure 1. The age- and sex-adjusted mean ratios of omega-3 PUFA mmol/100 mmol, omega-6 PUFA mmol/100 mmol, and the omega-3:omega-6 PUFA ratio at baseline, by individual criteria of the metabolic syndrome (i.e., the harmonized National Cholesterol Education Program Adult Treatment Panel III criteria), and metabolic syndrome diagnosis among 665 middle-aged Finnish subjects invited for health checkups in 1997–1998 and 2003–2004. A, waist criterion +/−; B, blood pressure criterion +/−; C, HDL criterion +/−; D, triglyceride criterion +/−; E, glucose criterion +/−; and F, metabolic syndrome diagnosis +/−. HDL, high density lipoprotein; PUFA, polyunsaturated fatty acid; +, positive; −, negative; ω, omega. Horizontal bars, 95% confidence interval.
The majority of circulating phospholipids are carried in the HDL cholesterol fraction. Our cross-sectional results revealed a significant relation between omega-3 and omega-6 PUFA mmol/100 mmol and HDL cholesterol and low HDL cholesterol concentrations, which is in agreement with the theoretical background (20).

Some intervention studies performed with relatively high doses of omega-3 PUFAs (1–2 g/day) have suggested that omega-3 PUFAs have a positive effect on lipoprotein profiles and that they may play a role in the course of the metabolic syndrome (8, 11, 12, 24). Similarly, the present study indicated that omega-3 PUFA mmol/100 mmol was inversely associated with the individual low HDL cholesterol criterion, but we could not determine a significant association between the change in the omega-3 PUFA mmol/100 mmol and the development of the metabolic syndrome (8, 11, 24). We did not have any specific omega-3 or omega-6 PUFA interventions in this study, so the natural changes in the omega-3 PUFA mmol/100 mmol might have been too small for the statistical power of this study. However, the increase in the omega-3 PUFA mmol/100 mmol mirrors the changes in diet, which are possibly linked to increased fish or fish oil intake or the use of omega-3 PUFA supplements. We did not collect exact food diaries in this study and could not evaluate the potential reasons for increased intake of omega-3 PUFAs. However, this finding suggests that the increase in the omega-3 PUFA mmol/100 mmol was not important for the development of metabolic syndrome at the population level, and this observation is in agreement with recent studies reporting that an increase in dietary omega-3 PUFAs was not associated with the future development of type 2 diabetes or cardiovascular events (25–27).

During the 6.4 years of follow-up, the changes in the omega-3 PUFA mmol/100 mmol and omega-6 PUFA mmol/100 mmol reflect a shift in the dietary fat consumption from hard to soft fats. This may be due to an intervention effect or related to more universal changes in dietary habits that have been reported in Finland (28).

Some individuals and groups have recommended substantial reductions in omega-6 PUFA intake (9, 11, 29). Our results of increased incidence of metabolic syndrome in subjects with reduced omega-6 mmol/100 mmol do not support these recommendations. The cross-sectional analysis in the present study indicated that the omega-6 PUFA mmol/100 mmol was inversely associated with the presence of individual metabolic syndrome criteria and metabolic syndrome, even after adjustment for covariates; this result is consistent with several previous findings (4, 6, 10, 30–32). Moreover, in our study, this result was repeatable and

![Figure 2](image-url). The age-, sex-, and baseline body mass index-adjusted associations between changes in the omega-3 (A) and omega-6 (B) mmol/100 mmol and the incidence of metabolic syndrome (i.e., the harmonized National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria) and its individual criteria after 6.5 years of follow-up among 482 middle-aged Finnish subjects without metabolic syndrome (MetS) at baseline in 1997–1998. BP, blood pressure criterion; glucose, glucose criterion; HDL, high density lipoprotein cholesterol criterion; PUFA, polyunsaturated fatty acid; TG, triglyceride criterion; ω, omega. □, no incident criterion; ■, the incident criterion; ▪, the incident criterion; □, no incident criterion. Vertical bars, 95% confidence interval.
similar when the data from the follow-up health checkup were used. In a longitudinal setting, increased omega-6 PUFA mmol/100 mmol correlated positively with HDL cholesterol and negatively with triglycerides and was also related to a lower incidence of metabolic syndrome. The incident metabolic syndrome criteria, such as low HDL cholesterol, high triglycerides, high fasting glucose, and high blood pressure, were inversely associated with the longitudinally decreased omega-6 PUFA mmol/100 mmol. In general, epidemiologic studies have reported that the dietary content of saturated fatty acids is positively associated with type 2 diabetes, while the dietary content of PUFAs is inversely associated with type 2 diabetes (33).

The increased intake of omega-3 PUFAs and the subsequently increased omega-3 PUFA:omega-6 PUFA ratio have been presented as a strategy to remediate metabolic syndrome (8–14). Our results do not support this assumption at the population level. In our study population, the omega-3 PUFA:omega-6 PUFA ratio was 1:8–10, which was lower than the recommended ratio of 1:1–4, reflecting a relatively low dietary intake of fish and fish oils in contrast to the plentiful dietary consumption of omega-6 PUFA-rich vegetable oils.

The mechanisms explaining the associations between serum and lipoprotein fatty acid content and glucose metabolism may also explain the effects of dietary fat quality on insulin sensitivity (4, 12, 13, 34). In insulin-resistant individuals, the lack of response to the insulin-stimulated, lipoprotein lipase-mediated hydrolysis of triglycerides from triglyceride-rich lipoproteins leads to an increased lifetime of triglycerides in circulation (35, 36). Diets rich in PUFAs result in attenuated postprandial responses of intestinally derived lipoproteins due to greater rates of clearance and greater activation of lipoprotein lipase, and individuals on diets rich in omega-6 PUFAs tend to have lower postprandial triglyceride levels (35, 36). Our results are in agreement with these findings.

The relatively small number of subjects in each group and the fact that there were only 2 health checkups are limitations of this study; however, a strength of this study is the longitudinal, population-based design. Furthermore, in contrast to most previous studies that used only estimates based on dietary diaries, the circulating serum fatty acid composition in this study was measured by nuclear magnetic resonance spectroscopy. Our results support the newly published recommendations of the American Heart Association that omega-6 PUFAs should be increasingly consumed in the diet (37).

ACKNOWLEDGMENTS

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Conflict of interest: none declared.

REFERENCES


