Differential effects of omega-6 and omega-3 fatty acids on telomere length

Dear Sir:

As the subject of aging receives increasing attention, much research is being devoted to the identification of biomarkers for age-related diseases. Leukocyte telomere length (LTL) is a focal point of this research. In the May issue of the Journal, Cassidy et al (1) examined associations between diet, lifestyle factors, and telomere length and concluded that “polyunsaturated fatty acid intake was negatively associated with LTL.” While their findings could have significant implications, their use of the term polyunsaturated fatty acid implies that all polyunsaturated fatty acids (PUFAs) were found to be negatively correlated with LTL, which was not the case. The conclusion of their study could therefore be inaccurate and regrettably misleading to its readers.

It must first be clarified that the term polyunsaturated fatty acid applies to 2 different types of fatty acids: omega-6 (n–6) and omega-3 (n–3). The n–6 and n–3 fatty acids are essential lipids that control and regulate many important bodily processes but are metabolically and functionally distinct and often have important opposing physiologic functions (2). For example, n–6 and n–3 fatty acids differentially modulate the production of key factors or mediators that regulate biological pathways such as inflammation and angiogenesis (3).

The conclusion of Cassidy et al’s study is inconsistent with the actual results of their data. In Table 3, the category of “polyunsaturated fatty acids” does appear to be significantly negatively correlated with LTL (quintile 5 compared with quintile 1: P = 0.002, P for trend = 0.02). However, PUFAs include the very different n–6 and n–3 fatty acids. The relevant categories listed in Table 3 are linoleic (n–3) and linoleic acids (n–6). n–6 Linoleic acid was also found to be negatively correlated with LTL (P = 0.001, P for trend = 0.046), but n–3 linoleic acid was not negatively correlated with LTL (P = 0.1, P for trend = 0.23). It is thereby clear that the P value of overall PUFAs is mainly derived from the value of n–6 linoleic acid. The question, then, is why Cassidy et al would choose to conclude that all PUFAs are negatively associated with LTL, rather than specifying n–6 fatty acids, as the data seem to indicate.

The absence of discussion about n–3 fatty acids in this article cannot be attributed to any lack of relevance to LTL. Telomeres are thought to be valid biomarkers of aging because they reflect cumulative oxidative stress and inflammation (4). Because n–6-derived metabolites are known to promote inflammation (5), it follows that an increase in n–6 fatty acid content would be associated with a decrease in LTL, as observed by Cassidy et al. Conversely, n–3 fatty acids and their metabolites may suppress oxidative stress and inflammation (3, 6). It is therefore possible that an opposite, positive correlation may exist between increased n–3 fatty acid intake and LTL. This has been supported by a recent study by Farzaneh-Far et al (7), which found that higher blood concentrations of marine n–3 fatty acids reduced the rate of telomere shortening over a period of 5 y. Such a differential effect of another PUFA should not be ignored. Because Cassidy et al did not distinguish between n–6 and n–3 PUFAs in the interpretation of their data, the validity of their conclusion is questionable.

My major concern is that Cassidy et al’s conclusion could likely mislead readers into avoiding all PUFAs, including n–6 and n–3 fatty acids, to reduce risk for age-related disease. In the past century, the industrial revolution and the emergence of agribusiness with processed foods, grain-fattened livestock, and hydrogenation of vegetable fats have considerably reduced the available content of n–3 fatty acids and increased that of n–6 fatty acids (8). As a result, modern Western diets are characterized by a highly imbalanced n–6:n–3 ratio (15–20:1), which has been thought to be associated with increased risk for many modern diseases (eg, heart disease and cancer) (2). Given the fact that n–3 fatty acids have multiple health benefits, governmental and scientific organizations now recommend an increased dietary intake of n–3 PUFAs (9). However, it can be inferred from the conclusion of Cassidy et al that all PUFA intake, including that of n–3 fatty acids, should be reduced to prevent LTL shortening. Consequently, the risk for age-related diseases, as well as other serious diseases, could actually be increased due to the reduction in n–3 PUFA intake.

In summary, the subject matter of Cassidy et al’s study is presently relevant, and the actual findings are interesting. However, the article was seriously weakened by the authors’ misinterpretation of the data and their neglect to mention n–3 fatty acids in context. Future studies related to PUFAs should recognize the differential roles of n–6 and n–3 fatty acids.

The author had no conflicts of interest to declare.

Jing X Kang

Laboratory for Lipid Medicine and Technology
Massachusetts General Hospital and Harvard Medical School
149 13th Street
Room 4433
Charlestown, MA 02129
E-mail: jxkang@partners.org

REFERENCES


doi: 10.3945/ajcn.110.000463.

---

**Reply to JX Kang**

Dear Sir:

Our cross-sectional study is one of the first studies to explore the potential relationships between dietary factors and telomere length (1). As Kang noted in the lengthy letter to the editor, polyunsaturated fatty acids (PUFAs) represent a family of many fatty acids that may have differential effects on telomere length. Thus, although exploratory, we clearly highlight throughout the text that the n–6 (omega-6) PUFA linoleic acid was inversely associated with leukocyte telomere length (LTL) in this study. We also clearly distinguished between n–3 (omega-3) and n–6 fatty acid intakes in Tables 1 and 3, and as shown in Table 1, no relation between omega-3 intake and LTL was observed. We are well aware of the interesting findings of Farzaneh-Far et al (2) in relation to blood concentrations of n–3 fatty acids and LTL, but in our multivariate models no relation between dietary n–3 intake and LTL was observed.

To put our findings on PUFAs and LTL in perspective, in our discussion we described the wealth of existing evidence on the protective effects of n–6 PUFAs in relation to cardiovascular disease (3) and highlighted that our findings were modest effects and merited further investigation.

Given the interest in LTL as a potential biomarker of aging and given the exploratory nature of our study, it will be interesting to further examine our findings in other observational studies.

Neither author had a conflict of interest to declare.

_Aedín Cassidy_

School of Medicine
University of East Anglia
Norwich
United Kingdom

_Eric B Rimm_

Departments of Epidemiology and Nutrition
Harvard School of Public Health
655 Huntington Avenue
Boston, MA 02115
E-mail: erimm@hsph.harvard.edu

---

**References**


---

**Intake of artificially sweetened soft drinks and risk of preterm delivery**

Dear Sir:

We are writing to comment on the article by Haldorsson et al (1). First, we wish to laud the authors for their clear writing. The prospective design and the very large sample size are study strengths. Although some of our concerns were expressed as potential weaknesses by the authors in their discussion, we wish to elaborate on several points that may compromise the study findings.

In the multivariate analysis, only pregravid body mass index was entered, but not weight gain during pregnancy nor presence of diabetes, which are potential confounders. It is entirely plausible that those women who had excessive weight gain during pregnancy may have been more predisposed to drinking noncaloric soda. Since only late preterm delivery, especially medically induced delivery, was associated with noncaloric soda intake, it is possible that those women who gained excessive weight and whose babies had macrosomia might have been more likely to be candidates for medically induced late preterm delivery? This possibility cannot be ruled out.

Only soda beverages with noncaloric sweeteners were considered in this study. Yet, noncaloric sweeteners are also used extensively in tea, coffee, and other foods and beverages. Thus, the data limited to soda drinking are incomplete and potentially introduce bias.

The gestational period was examined as a categorical rather than a continuous variable. The latter approach would have led to a more robust statistical analysis. Greater error could have been introduced by misclassification.

The design of this study is cohort. Yet, the results are presented as odds ratios rather than relative risk, which is a standard measure of risk in cohort studies. It appears that this choice was made to estimate relative risk because the outcomes in this study were infrequent. The use of odds ratios in this very large-scale cohort study reinforces the fact that the overall association between diet soda intake and preterm delivery was based on small outcome number and thus, the associations were relatively weak although statistically significant.

In observational studies such as this, applying the Hill criteria for assessing disease causation can help gain further insight into the nature of the relation found (2).

For sake of brevity, only salient points are outlined below: