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Marklund M, Wu JHY, Imamura F, et al. Biomarkers of Dietary Omega-6 Fatty Acids and Incident Cardiovascular Disease and Mortality. Circulation. 2019;139(21):2422-2436.

What We Know, Think We Know, or Are Starting to Know

We know from the very early work of George and Mildred Burr, who discovered essential fatty acids [EFAs], that we lack the capability to synthesise EFAs endogenously, and therefore require a dietary source. Of those EFAs, you won' t generally hear anything but positives about omega-3 fatty acids. But mention omega-6 linoleic acid [LA] and, to quote The Joker, everyone just loses their minds.*

***Figure** from Bale & Ledger (2008) illustrating effect size of hysteria when discussing omega-6 vegetable oils with low-carb enthusiasts. The left and right hands represent 95% Confidence Intervals.*

In the 1950' s, tightly controlled metabolic ward studies indicated that polyunsaturated fats led the most pronounced reductions in blood cholesterol levels [1-5]. More particularly, these studies indicated that replacing saturated animal fat in the diet with LA-rich oils led to significant improvements in blood cholesterol levels [1-5]. With the understanding of the risk for heart disease caused by elevated cholesterol, the earliest dietary advice to reduce heart disease risk emphasised replacing saturated fats with polyunsaturated fats.

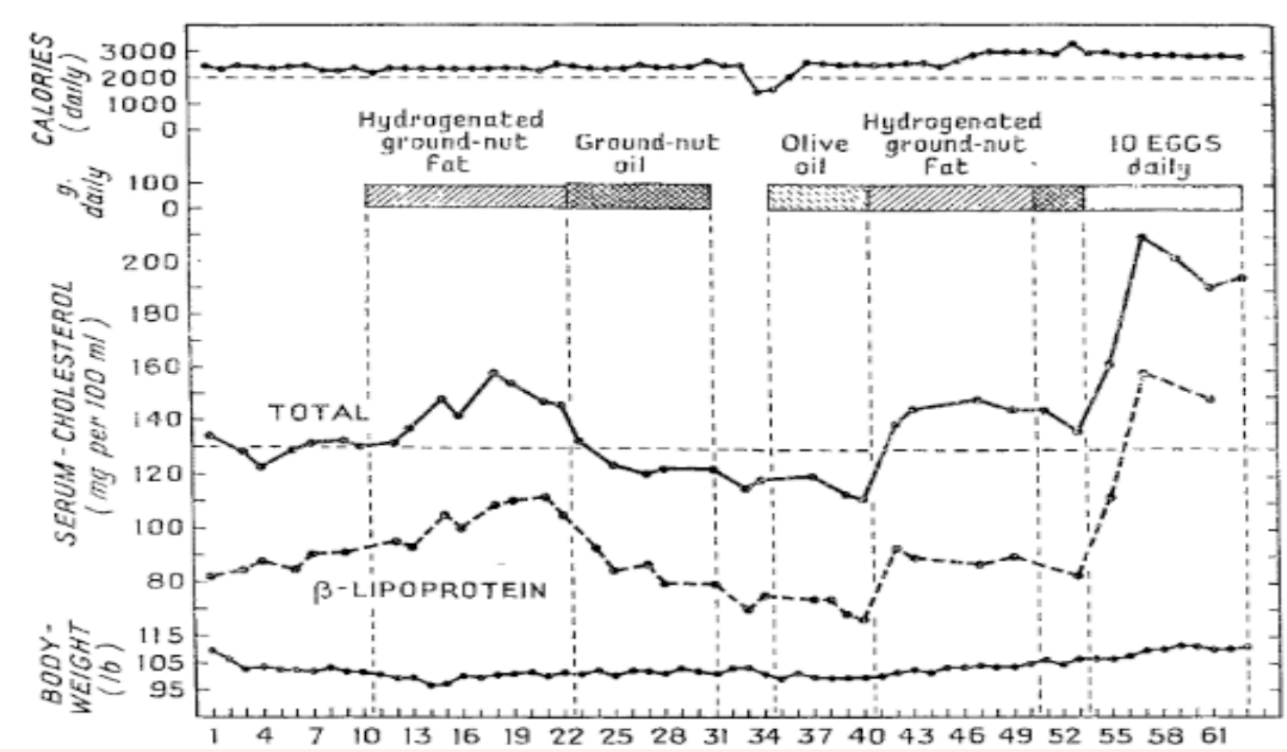
However, this has not been without controversy. Some researchers have argued that increasing omega-6 LA levels in the 'Western diet' have contributed to adverse health outcomes [6]. The omega-6:omega-3 ratio has been suggested to be excessive in modern diets, relative to evolutionary diets [6].

Despite these suggestions, however, comparing high vs. low intakes of LA has been associated with a 14% reduction in risk for coronary heart disease [CHD] events, and 17% reduction in risk for CHD death, in analysis of both the Nurses' Health Study and Health Professionals Follow-Up Study cohorts [7]. In a pooled analysis of 11 cohorts, substituting 5% of energy from saturated fat with LA was associated with a 13% reduction in CHD mortality among 11 cohort studies [8].

The use of biomarkers in nutritional epidemiology, where possible, provides a more objective means of reflecting dietary intake. The most commonly used biomarkers, which measure the concentration of a nutrient in a plasma, red blood cells, or adipose tissue, are known as "concentration biomarkers", as they measure the concentration of that particular nutrient in the circulation or tissue. The present study analysed circulating blood and adipose tissue concentrations of LA, and examined the relationship between these biomarkers of LA intake and cardiovascular disease risk.

*Geek Box: Omega-6 Fats and Hysteria

Linoleic acid is an 18-carbon polyunsaturated fatty acid with two double-bonds, with the first double-bond occurring in the 6th position in the chain, known as the 'omega'. Thus, the fatty acid nomenclature that you will see written is 18:2n-6, and is more commonly referred to as 'omega-6 fat'. LA commonly occurs in many vegetable oils, nuts, seeds, and whole grains. LA also has been found in industrialised food products, including baked goods, confectionary, and margarines and shortenings. As early as the metabolic ward studies of the 1950s, it was evident that hydrogenation of vegetable oil fats had a negative effect on blood cholesterol levels. In a study published in the Lancet in 1956, Bronte-Stewart et al. (4) alternated between feeding participants natural groundnut oil and hydrogenated groundnut oil, and notice diametrically opposed effects of the same oil on blood cholesterol levels, based on whether the oil was hydrogenated: natural groundnut oil decreased cholesterol levels, while hydrogenated groundnut oil increased cholesterol significantly [Figure from study below]. With hindsight, we understand that the process of hydrogenation created trans-fats, however, the point is that from the perspective of cardiovascular health, this was technically evident as early as the 1950's. Nonetheless, with the food industry responding to public health recommendations to replace saturated fats with polyunsaturated fats, hydrogenation was ubiquitous at the time - a case of research not necessarily translating into industry, which remains an issue to this day. The result was that many foods nominally labelled as 'PUFA' or 'omega-6' in fact contained high amounts of trans-fats; omega-6 have been guilty by association ever since, with many of the claims made currently - of causing inflammation or increasing heart disease risk - stemming from research in the '60s where LA is confounded by trans-fats. This view of LA is ingrained in many areas of thinking, particularly 'ancestral' health circles who often emphasis 'natural fats', i.e., animal fats, but seemingly not realising or acknowledging that LA is essential, or realising that it is as 'natural' as any other fat found in nature.



The Study

The Fatty Acid and Outcome Research Consortium [FORCE] of studies comprises over 30 cohorts in which measurements of circulating or adipose tissue fatty acids have been conducted, together with confirmed chronic disease event outcomes.

Studies were included in the primary analysis if they measured levels of linoleic acid [LA] and arachidonic acid [AA], and reported cardiovascular disease [CVD] endpoints: total CVD, CVD mortality, ischemic stroke, and coronary heart disease [CHD] mortality. The compartments measured for LA and AA included red blood cells [erythrocytes], plasma phospholipids, cholesterol, total plasma, and adipose tissue.

The results of each individual study were pooled* for analysis, which was conducted by pooling all fatty acid compartments together [overall analysis], and pooled for each specific compartment measured.

To compare results and allow for pooling of study results, the interquartile range of the concentration of LA and AA was used for each study - this is the range between the midpoint of the lowest quintile and midpoint of highest quintile, yielding a given value [i.e., if the midpoint of the highest quintile was 10%, and the midpoint of the lowest quintile was 3%, the interquartile range would be 7%]. An analysis of each compartment was also undertaken using the absolute levels of LA and AA as a percentage of total fatty acids, as the exposure. Hazard ratios [HR] were calculated to estimate risk of CVD outcomes according to differing interquartile ranges of LA and AA, and according to percentage of total fatty acids.

*Geek Box: Pooled Analysis

You'll have come across meta-analysis over and over in reading research, but a pooled analysis is same-same-but-different. Both meta and pooled analysis are similar insofar as they are condensing multiple published studies into an overall analysis, to obtain a summary of the effect of an exposure on an outcome of interest. In a meta-analysis, the results of each primary study are included, and the analysis is conducted by combining all of these results together to obtain a single summary estimate of the overall effect. This is an attractive methodology where the primary included studies are relatively similar in design, and where the exposure is similar in dose, two criteria that are more easily met in medical interventions. A pooled analysis is another method of summarising results, but rather than use the overall result of the primary study, use the individual data from the participants in that study, and combine - 'pool' - all of this individual data together. This provides increased statistical power, and allows for testing different aspects of the relationship between an exposure and outcome by doing sensitivity analysis [i.e., testing a specific variable within an overall analysis on the outcome], performing sub-group analysis [i.e., studies with >10yrs follow-up or studies with women only], and investigating dose-responses. Pooling itself if all individual data is just all lumped together can yield spurious results. Thus, just like meta-analysis, real care must be taken in the methodology, and the studies included must have clear inclusion/exclusion criteria, similar laboratory analysis methods for the primary data and biomarkers measured, and the data must be standardised for analysis. If these criteria can be met, then pooling individual data together can, in effect, act as one very large cohort [vs. combining individual study results, where smaller studies may be considered less reliable].

Results: The pooled data included 76,356 fatty acid measurements from 68,659 participants, across 13 countries. Median follow-up periods ranged from 2.5yrs to 31.9yrs, in which there was 10,477 total incident CVD events, 4,508 CVD deaths, 11,857 incident CHD events, and 3,705 incident ischemic strokes.

In the interquartile range analysis, higher LA levels were association with the following:

- 7% [HR 0.93, 95% CI 0.88-0.99] reduction in risk for total CVD
- 22% [HR 0.78, 95% CI 0.70-0.85] reduction in risk for CVD mortality
- 12% [HR 0.88, 95% CI 0.79-0.98] reduction in risk for ischemic stroke

In the high vs. low quintile analysis, the highest levels of LA were associated with a 23% [HR 0.77, 95% CI 0.69-0.86] reduction in risk for total CVD.

Total plasma AA was associated with a significant 19% [HR 0.81, 95% CI 0.70–0.94] reduction in risk for total CVD in the interquartile range analysis. This effect was similar comparing the highest vs. lowest quintile of total plasma AA, which resulted in a significant 21% [HR 0.79, 95% CI 0.67-0.93] reduction in risk for total CVD. In the high vs. low analysis, combining overall AA, i.e., AA measures from all compartments, was associated with a significant 8% [HR 0.92, 95% CI 0.86-0.99] reduction in total CVD risk.

These associations for both LA and AA did not significantly differ according to subgroups defined by age, sex, race, omega-3 PUFA levels, diabetes status, statin use, aspirin use, or baseline year of fatty acid measurement.

The Critical Breakdown

Pros: All studies participating in FORCE used the same, prespecified analysis protocol with inclusion/exclusion criteria, required for a pooled analysis. The pooled analysis included a large number of fatty acid measures and participants, and number of CVD events.

Cons: Adipose tissue measures were only used in 3 studies. Despite the pooling of data from 13 countries and 4 continents, the overwhelming majority of participants in cohorts were White/Caucasian. Most individual studies measured a specific fatty acid compartment [rather than multiple], and thus no meaningful comparisons between compartments - adipose tissue vs. red blood cells - could be conducted.

Key Characteristic

Use of biomarkers for LA, which provide a reliable, and extensively researched, indication of dietary LA intake [(9)]. Numerous analysis have shown that increasing dietary intake of LA increases the measurements of LA in various compartments, whether red blood cells, cholesterol, phospholipids, or adipose tissue [although the magnitude of increase differs in different compartments] [(9)]. Adipose tissue concentrations reflect the previous 1-2yrs of dietary intake, which is significantly longer than the 4-months that red blood cells reflect [(9)]. Thus, this study provided an objective in vivo measure of levels of LA and AA, which reflects a range of dietary intakes over both the short, intermediate, and long term.

Interesting Finding

While the overall analysis in relation to AA was neutral, the association of reduced risk for total CVD from circulating plasma AA is interesting given the negative assumptions made about LA and AA.

LA can be metabolised to AA, and AA acts as the precursor to potentially pro-inflammatory mediators: this has always formed the basis for suggesting that omega-6 fats increase inflammation.

However, dramatically altering LA levels does not change circulating [i.e., plasma] levels of AA; a systematic review illustrated that increasing LA by up to 551% from baseline, or reducing LA by up to 90%, did not result in any change in circulating concentrations of AA [10]. In a previous 2014 analysis of the relationship between circulating fatty acids and CHD, circulating AA levels were associated with a 17% [RR 0.83, 95% CI 0.74–0.92] reduction in risk [11]. Ultimately, it seems like the hysteria over AA is unwarranted, and at the very least circulating AA either have a neutral effect on CVD risk, or even related to a reduction in risk.

Relevance

And thus, we come full circle.

In 2013, a research group published a meta-analysis which reanalysed a number of studies from the 1960s and 1970s, including the Sydney Diet-Heart Study, and purported to find an increase in heart disease risk from LA [12]. However, you' ll recall the issue with these studies from above. Omega-6 LA has remained controversial, due to the hangover from studies like the Sydney Diet-Heart Study and others, where the PUFA supplementation arm included margarines with high trans-fat content.

While no body of evidence is even 100% conclusive, the importance of a study like this cannot be underestimated, given the "vegetable-oil-industry-paid-big-pharma-to-poison-us" narratives that abound about omega-6 polyunsaturated LA, and the purported mechanism that LA = AA = inflammation = CVD.

Even if AA = inflammation were to be true, there is no evidence that dramatic changes in dietary LA intake alter circulating levels of AA [10]. And, there is virtually no evidence that increasing dietary LA increases inflammatory markers in humans [13]. In fact, there is even evidence that LA intervention diets reduce high-sensitivity C-reactive protein [14].

Once we park the issue of food-source confounding with trans-fats from the 1960s, it starts to become more clear that LA-rich foods exert a benefit for CVD risk. By conducting an analysis of biomarkers of LA intake, i.e, objective in vivo measures of fatty acids, this study adds a level of certainty from epidemiology, where an RCT with thousands of participants and objective measures of diet would be infeasible [15]. There are now multiple lines of evidence - metabolic ward, prospective cohort studies assessing dietary intake, cohort studies assessing biomarkers, and interventions examining inflammatory markers - all converging to dispel the hysteria around LA and heart health.

Application to Practice

Release omega-6s from purgatory. Dietary patterns enriched in nuts, seeds, vegetable oils, and wholegrains, correlated with higher LA intake, and the various lines of evidence point to LA reducing risk for CVD.

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