Published in final edited form as:

Circulation. 2015 July 21; 132(3): e25–e26. doi:10.1161/CIRCULATIONAHA.115.014853.

Response to 1) Sertoglu et al – proper use of fatty acid levels to assess cardiovascular health, and 2) Lucas – n6/n3 ratio and health: what is the usefulness of a good divided by good?

Jason HY Wu, PhD[1], **Rozenn N. Lemaitre, PhD, MPH**[2], **Irena B. King, PhD**[3], **Xiaoling Song, PhD**[4], **Bruce M Psaty, MD, PhD**[2,5,6,7], **David S. Siscovick, MD, MPH**[8], and **Dariush Mozaffarian, MD, DrPH**[9]

[1]George Institute for Global Health, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia

[2]Cardiovascular Health Research Unit, Department of Medicine University of Washington, Seattle, WA

[3]Department of Internal Medicine, University of New Mexico, Albuquerque, NM

[4]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[5]Department of Epidemiology, University of Washington, Seattle, WA

[6]Department of Health Services, University of Washington, Seattle, WA

[7]Group Health Research Institute, Group Health Cooperative, Seattle, WA

[8]New York Academy of Medicine, New York, NY

[9]Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA

Sertoglu and colleagues express concern about measurement of circulating fatty acid biomarkers in plasma. However, our investigation did not measure fatty acids in total plasma (the sum of fatty acids in non-esterified fatty acids, cholesterol esters, triglycerides, and phospholipids), but in the plasma phospholipid fraction. The plasma phospholipid fraction reflects fatty acid concentrations in cell membranes. Furthermore, phospholipid fatty acids in plasma and erythrocyte membranes inter-exchange, reflect fatty acid consumption over a similar period of time, and are reasonably correlated.[1] Thus, either plasma phospholipid or erythrocyte fatty acid composition is a valid and reliable biomarker of dietary consumption. This explains why numerous longitudinal investigations have evaluated associations of fatty acids in plasma phospholipids or erythrocyte phospholipids in relation to cardio-metabolic disease risk.[2, 3]

We appreciate Sertoglu's interest in omega-3 polyunsaturated fatty acids (n-3 PUFA). As described and cited in the present investigation, we previously measured and reported

Corresponding author and request for reprints: Jason Wu, Level 10, King George V Building, 83-117 Missenden Rd, Camperdown, NSW 2050, Australia, Phone: +61-2-9993-4500, jwu1@georgeinstitute.org.au.

Disclosures

The other authors report no conflicts.

associations between plasma phospholipid n-3 PUFA biomarkers and risk of total and cardiovascular mortality in this cohort.[4] In addition, in the current investigation we evaluated and found little evidence of interaction between linoleic acid (the major dietary omega-6 fatty acid) and n-3 PUFA (P=0.54). Indeed, our findings suggested an additive benefit, in that those with highest levels of both linoleic acid and n-3 PUFA had the lowest risk of total and cardiovascular mortality (figure 3, supplement figure 2).[5] This important finding would have been obscured using an analysis based on the n-6/n-3 ratio. The conceptual and biologic flaws of the n-6/n-3 ratio have been described.[6] A key flaw is the inability to discern very different conditions of dietary intake or underlying physiology: e.g., a ratio may be identical when consumption and circulating levels of both n-6 and n-3 are high or when both are low, two very different circumstances. In addition, the ratio cannot distinguish increases in the n-6 PUFA vs. decreases in n-3 PUFA. Finally, the conceptual basis of the ratio depends on the notion that n-6 PUFA and n-3 PUFA have opposing effects. However, substantial evidence indicates that both are beneficial;[6] indeed, a recent meta-analysis found that individuals with higher circulating levels of arachidonic acid, the prototypical n-6 PUFA thought to be pro-inflammatory and harmful, had lower risk of coronary disease.[7] Given these considerations, we agree with Dr Lucas that existing evidence suggest beneficial effect of dietary linoleic acid for cardiovascular outcomes, not harm, and use of the n-6/n-3 ratio is unlikely to impart meaningful information over and above assessment of the individual fatty acids alone.

Acknowledgments

Dr. Mozaffarian reports ad hoc travel reimbursement or honoraria from Bunge, Pollock Institute, Quaker Oats, and Life Sciences Research Organization; ad hoc consulting fees from McKinsey Health Systems Institute, Foodminds, Nutrition Impact, Amarin, Omthera, and Winston and Strawn LLP; membership, Unilever North America Scientific Advisory Board; royalties from UpToDate; and research grants from the National Institutes of Health.

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