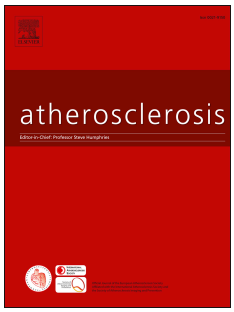
Accepted Manuscript



Redefining target Omega-3 index levels: The Japan public health center study

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PII: S0021-9150(18)30026-1

DOI: 10.1016/j.atherosclerosis.2018.01.030

Reference: ATH 15353

To appear in: *Atherosclerosis*

Received Date: 3 January 2018

Accepted Date: 17 January 2018

Please cite this article as: Harris WS, Redefining target Omega-3 index levels: The Japan public health center study, *Atherosclerosis* (2018), doi: 10.1016/j.atherosclerosis.2018.01.030.

Redefining Target Omega-3 Index Levels: The Japan Public Health Center Study

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According to international data compiled by the American Heart Association, the rate of death (per 100,000 people) from coronary heart disease (CHD) in 2011 in Japan was 47 and in the US, 132.[1] This marked difference was shown many years ago to not have a genetic basis[2], and thus can only be attributable to environmental factors. Smoking rates are higher in Japan than the US[3], and hypertension is more prevalent[4], so these two risk factors clearly cannot explain lower CHD rates in Japan vs. the US. Diet is an obvious possibility, but which component(s)? Total calorie intakes are much lower in Japan than in the US, and, as a percent of calories, so is the fat intake; but carbohydrate intake is higher[5]. Another major difference between US and Japanese diets is the much greater intake in Japan of the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) compared with the US (approximately 900 mg/d[6] vs 100 mg/day[7]). Given the known cardioprotective effects of these FAs[8, 9], many studies have examined the associations between the *intake* of omega-3 FAs and risk for CHD in Japan, but few have used circulating FA *biomarkers* as their exposure variable. In that light, the report by Hamazaki et al. in this issue of Atherosclerosis is illuminating[10].

These investigators utilized the Japan Public Health Center (JPHC) Study dataset to identify incident cases of CHD and matching controls, and then examined the extent to which plasma phospholipid levels of EPA, DHA and the FA intermediate between these two, docosapentaenoic acid (DPA), were associated with risk for CHD events. The study included 209 cases and 418 controls. Follow-up was for 13.5 years. They reported that higher levels of omega-3 FAs (EPA+DHA+DPA) were associated with lower risk for sudden cardiac death and fatal CHD, but not with total CHD events. This relationship with fatal more than non-fatal disease is a recurring theme in this area[11, 12].

It is important to pause here to consider just how different the Japanese are from their US counterparts in terms of omega-3 levels. Hamazaki et al. referred to the Multi-Ethnic Study of Atherosclerosis (MESA) cohort in the US as being generally similar to theirs. A study from MESA[13] that also used plasma phospholipid omega-3 levels to predict risk for cardiovascular disease (CVD) endpoints reported FA levels by quartiles, just as Hamazaki et al. did. And just as the Japanese group found significant inverse relationships between omega-3 levels and coronary outcomes, so too did the US investigators. But consider the range of omega-3 levels across which differences in cardiac events were observed. The *highest* quartiles for both EPA and DHA in the US study were similar to the *second* quartiles in the Japan study (Figure 1). To put the values into context, the plasma phospholipid levels of long chain omega-3 FAs can be converted into a more familiar metric of omega-3 status, the Omega-3 Index (erythrocyte EPA+DHA[14]), using previously described equations[15]. Focusing on the current cardioprotective target value for the Omega-3 Index of 8% or more[15], in the Japanese cohort the second quartile's mean index was just over 8% whereas even the fourth quartile's mean was not quite this high in the US study (Figure 2). With a median Omega-3 Index of 9% (versus 5.3% in the US cohort), most of the Japanese participants were already in a desirable zone. The question that Hamazaki et al. are essentially asking is this: "Can risk for fatal CHD events be reduced even more at even higher Omega-3 Index levels?" or, "Is 8% the right target level for the Japanese?" Their data suggest that the answers are "yes" and "probably not," respectively. Exactly where this benefit would plateau – as it surely must - is still uncertain, but Japanese at 10% appear to have a lower risk for fatal CHD than those at 8%.

Another interesting finding in this report is that DPAn-3 levels were not associated with CV outcomes. This confirms our recent findings in the Women's Health Initiative Memory Study[16] as regards CVD death (but DPA was inversely associated with total mortality.) Others, however, have reported favorable relations for this omega-3 FA and CVD death[17]. It is possible that in the context of a high Omega-3 Index, DPA levels become relatively irrelevant, but in Western settings with a low EPA and DHA level, DPA may play a favorable role. Somewhat surprisingly, DPA levels were essentially the same in the plasma of this Japanese and the MESA cohorts (Figure 1). The factors that influence DPA levels, and what the levels of this poorly-studied omega-3 FA mean will require further study.

Surprisingly smoking was not significantly related to CHD outcomes, but only in individuals with higher omega-3 status; it was in those with lower levels. This confirms an observation first made in 1996 in the Honolulu Heart Study[18]. The implication of this is that high omega-3 intakes (and thus blood levels) may protect the heart against the harmful effects of cigarette smoke. We have observed in at least two Western cohorts that smokers have lower omega-3 levels than non-smokers[19, 20], but whether this is due to a lower fish intake by smokers or direct destruction of the omega-3 FAs by components of smoke *in vivo* is not clear. How omega-3 levels may have varied by smoking status in the JHPC study was not reported, but it could be that an average Omega-3 Index of nearly 10% may somewhat blunt the adverse effects of smoking. If so, this effect could be mediated via the anti-inflammatory effects of EPA and DHA[21, 22].

The take-home message of this study in the JHPC population is that an Omega-3 Index of 8% is not really the optimal level, at least as it relates to risk for fatal CHD. It could be that 10% - at least for this population – ought to be the target level. Further studies to explore this hypothesis, especially in Western populations, should be a high priority. At present there is a major randomized controlled trial that is testing the effects of 3.4 g/d of EPA+DHA on CVD outcomes in hypertriglyceridemic patients on background statin therapy. The Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (NCT02104817) should produce an average Omega-3 Index of about 10% in the active arm of this trial[23], and hence it will provide the first test of this hypothesis.

Figure Legends

Figure 1. Comparison of the plasma phospholipid n-3 fatty acid quartiles in the US-based Multi-Ethnic Study of Atherosclerosis (MESA) and the Japan Public Health Center study (JPHC). Note that eicosapentaenoic acid (EPA; C20:5n3) and docosahexaenoic acid (DHA; C22:6n3) differ markedly between cohorts, but docosapentaenoic acid (DPA; C22:5n-3) does not.

Figure 2. Estimated Omega-3 Index (erythrocyte EPA+DHA) by Quartile in in the US-based Multi-Ethnic Study of Atherosclerosis (MESA) and the Japan Public Health Center study (JPHC).

References

[1] Mozaffarian, D, Benjamin, EJ, Go, AS, et al., Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association, Circulation, 2015;131:e29-e322.
[2] Robertson, TL, Kato, H, Rhoads, GG, et al., Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Incidence of myocardial infarction and death from coronary heart disease, Am J Cardiol, 1977;39:239-243.
[3] Ng, M, Freeman, MK, Fleming, TD, et al., Smoking prevalence and cigarette consumption in 187 countries, 1980-2012, JAMA, 2014;311:183-192.
[4] Collaboration, NCDRF, Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants, Lancet (London, England), 2017;389:37-55.
[5] Zhang, R, Wang, Z, Fei, Y, et al., The Difference in Nutrient Intakes between Chinese and Mediterranean, Japanese and American Diets, Nutrients, 2015;7:4661-4688.
[6] Iso, H, Kobayashi, M, Ishihara, J, et al., Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I, Circulation., 2006;113:195-202.
[7] Papanikolaou, Y, Brooks, J, Reider, C, et al., U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003-2008, Nutrition journal, 2014;13:31.
[8] Endo, J and Arita, M, Cardioprotective mechanism of omega-3 polyunsaturated fatty acids, Journal of cardiology, 2016;67:22-27.
[9] Khawaja, OA, Gaziano, JM and Djousse, L, N-3 fatty acids for prevention of cardiovascular disease, Current atherosclerosis reports, 2014;16:450.
[10] Hamazaki, K, Placeholder, Atherosclerosis, 2018;XX:xx-xx.
[11] Alexander, DD, Miller, PE, Van Elswyk, ME, et al., A Meta-Analysis of Randomized Controlled Trials and Prospective Cohort Studies of Eicosapentaenoic and Docosahexaenoic Long-Chain Omega-3 Fatty Acids and Coronary Heart Disease Risk, Mayo Clinic proceedings, 2017;92:15-29.
[12] Chowdhury, R, Warnakula, S, Kunutsor, S, et al., Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis, Annals of internal medicine, 2014;160:398-406.
[13] de Oliveira Otto, MC, Wu, JH, Baylin, A, et al., Circulating and Dietary Omega-3 and Omega-6 Polyunsaturated Fatty Acids and Incidence of CVD in the Multi-Ethnic Study of Atherosclerosis, Journal of the American Heart Association, 2013;2:e000506.
[14] Harris, WS and von Schacky, C, The Omega-3 Index: a new risk factor for death from coronary heart disease?, Prev Med, 2004;39:212-220.
[15] Harris, WS, Del Gobbo, L and Tintle, NL, The Omega-3 Index and relative risk for coronary heart disease mortality: Estimation from 10 cohort studies, Atherosclerosis, 2017;262:51-54.
[16] Harris, WS, Luo, J, Pottala, JV, et al., Red blood cell polyunsaturated fatty acids and mortality in the Women's Health Initiative Memory Study, J Clin Lipidol, 2017;11:250-259.
[17] Del Gobbo, LC, Imamura, F, Aslibekyan, S, et al., omega-3 Polyunsaturated Fatty Acid Biomarkers and Coronary Heart Disease: Pooling Project of 19 Cohort Studies, JAMA internal medicine, 2016;176:1155-1166.
[18] Rodriguez, BL, Sharp, DS, Abbott, RD, et al., Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. The Honolulu Heart Program, Circulation, 1996;94:952-956.

[19] Block, RC, Harris, WS and Pottala, JV, Determinants of Blood Cell Omega-3 Fatty Acid Content, Open Biomarkers J, 2008;1:1-6.
[20] Harris, WS, Pottala, JV, Lacey, SM, et al., Clinical correlates and heritability of erythrocyte eicosapentaenoic and docosahexaenoic acid content in the Framingham Heart Study, Atherosclerosis, 2012;225:425-431.
[21] Fontes, JD, Rahman, F, Lacey, S, et al., Red blood cell fatty acids and biomarkers of inflammation: A cross-sectional study in a community-based cohort, Atherosclerosis, 2015;240:431-436.
[22] Calder, PC, Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance, Biochimica et biophysica acta, 2015;1851:469-484.
[23] Maki, KC, Bays, HE, Dicklin, MR, et al., Effects of prescription omega-3-acid ethyl esters, coadministered with atorvastatin, on circulating levels of lipoprotein particles, apolipoprotein CIII, and lipoprotein-associated phospholipase A2 mass in men and women with mixed dyslipidemia, J Clin Lipidol, 2011;5:483-492.