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Choosing foods to balance competing n-3 and n-6 HUFA and their actions

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Abstract – Many enzymes metabolizing essential fatty acids (EFA) do not discriminate much between the n-3 and n-6 structures. Thus, relative abundances of competing n-3 and n-6 acids influence relative rates of reaction during hydrolysis, activation, elongation, desaturation and acyl transfer that control the balance of n-3 and n-6 highly unsaturated fatty acids (HUFA) accumulated in tissues. An empirical competitive, hyperbolic equation describes how dietary EFA maintain tissue HUFA balance. The %n-6 in HUFA is a useful biomarker for average dietary intakes of n-3 and n-6 EFA. An Omega 3-6 Balance Score combines data on eleven competing EFA in a food and expresses them as a single number. Average daily food scores range from –7 to +2, relating to HUFA balances from 81% to 30% n-6 in HUFA. The HUFA released by phospholipase provide substrates that form important hormone-like bioactive lipids. Formation and action is more intense with n-6 than n-3 mediators, allowing n-6 eicosanoids to shift healthy physiology toward pathophysiology for people who have a high proportion of n-6 arachidonate in tissue HUFA. The HUFA balance, expressed as the %n-6 in HUFA, is a useful biomarker for health risk assessment. The biomarker makes evident that, in the absence of dietary n-3 nutrients, dietary n-6 linoleate has a very narrow therapeutic window, and it can be widened by dietary n-3 nutrients. A useful concept for preventive nutrition is to NIX the 6 while you EAT the 3.

Keywords: Arachidonate / eicosanoids / highly unsaturated fatty acids (HUFA) / omega-3 / omega-6

Résumé – Choisir ses aliments pour rééquilibrer le ratio entre (n-3) et (n-6) et leurs effets sur la santé de l'Homme. De nombreuses enzymes métabolisant les acides gras polyinsaturés (AGPI) essentiels-ne font pas complètement la distinction entre les structures en n-6 et en n-3. Ainsi, ce sont les abondances relatives entre les AGPI n-3 et n-6 qui conditionnent leur taux respectif de métabolisation, mettant en jeu des réactions d'hydrolyse, d'activation, d'allongement, de désaturation et d'acylation qui contrôlent, par contrecoup, l'équilibre entre les AGPI à longue chaîne (AGPI-LC) en n-3 et n-6 s'accumulant dans les tissus. Une équation hyperbolique empirique de compétition décrit comment l'apport régime alimentaire en AGPI essentiels maintient cet équilibre tissulaire en AGPI-LC. Le pourcentage des n-6 dans les AGPI-LC totaux est un biomarqueur pertinent du niveau moyen de consommation alimentaire en AGPI essentiels n-3 et n-6. Un score de ratio entre les oméga 3 et 6 a été établi en combinant les données de onze AGPI concurrents présents dans les aliments. Les scores moyen des aliments s'échelonne entre −7 et +2, pour des valeurs d'AGPI-LC n-6 (en % des AGPI-LC totaux) comprises entre 81 % et 30 %. Les AGPI-LC tissulaires libérés par action de la phospholipase fournissent des substrats de médiateurs lipidiques bioactifs. Leur production et leur activité s'avèrent plus intenses lorsqu'ils dérivent de la série n-6. Elles peuvent être ainsi à l'origine d'une situation potentiellement physiopathologique chez les personnes dont les teneurs tissulaires en AGPI-LC n-6 et en acide arachidonique sont particulièrement élevées (situation de déséquilibre n-6/n-3). L'équilibre entre les 2 familles d'AGPI, exprimé par le pourcentage de n-6 dans les AGPI-LC totaux, est alors un biomarqueur pertinent dans l'évaluation du risque pour la santé de l'Homme. À partir de ce biomarqueur, il est établi qu'en l'absence d'AGPI n-3 dans le régime alimentaire, l'apport en AGPI essentiels n-6 sous la forme d'acide linoléique possède une fenêtre d'effet thérapeutique très étroite, fenêtre qui peut être élargie par un régime alimentaire riche en n-3. Le concept en terme de nutrition préventive serait de réduire la consommation des n-6 et de favoriser celle des n-3 (« *to NIX the 6 while you EAT the 3* »).

Mots clés : Archidonate / AGPI / oméga 3 / oméga 6

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Highlights

– Relative abundances of n-3 and n-6 nutrients control the balance of accumulated n-3 and n-6 highly unsaturated fatty acids (HUFA).
– High proportions of n-6 arachidonate in tissue HUFA tend to shift healthy physiology toward pathophysiology.
– A useful concept for preventive nutrition is to NIX the 6 while you EAT the 3.

1 Introduction

Competition is a dominant theme in the multi-enzyme metabolism that converts 18-carbon polyunsaturated fatty acids (PUFA) into 20- and 22-carbon highly unsaturated fatty acids (HUFA). Chain length and the number of double bonds influence rates for some hydrolase, desaturase, elongase and acyltransferase activities, but few of these reactions respond to n-3 and n-6 structural difference. A consequence of similar reactivity for competing n-3 and n-6 structures is that the relative abundance of an n-3 or n-6 substrate dominates the relative balance of n-3 and n-6 HUFA accumulated in tissues. Because n-3 and n-6 essential fatty acids (EFA) only appear in humans from dietary supplies, people's voluntary food choices have a major influence on the balance of n-3 and n-6 HUFA that accumulate in tissues. When it became evident that the tissue HUFA balance influences the intensity of formation and action of potent hormone-like eicosanoids, it seemed useful to examine quantitative details by which the supply of dietary EFA affects the accumulated HUFA balance.

2 How diet affects tissue HUFA balance

Increased intake of the two major dietary EFA, linoleate and linolenate, expressed as percent of food energy (en%), gave linearly increased weight percent (wt%) contents among the triglyceride acids in plasma, liver and adipose with wt% = $C_x X$en% S (Lands *et al.*, 1990). The observed value of C_x for rats was 2.9 for linoleate (18:2 n-6) and 1.8 for linolenate (18:3 n-3). When volunteer groups of Chicago residents were studied later (Lands *et al.*, 1992), similar observed values for C_x (2.8 for 18:2 n-6 and 1.3 for 18:3 n-3) indicated similar dynamics for triglyceride metabolism in rats and humans. The simple linear relationship between diet and tissue triglyceride allows the composition of fasting plasma triglycerides to be a useful indicator of the average en% of ingested 18:2 n-6 and 18:3 n-3. Figure 1 illustrates the flow of acids from the diet among plasma, liver and adipose lipids by way of plasma nonesterified fatty acids (NEFA). In general, the daily intermittent entry of essential fatty acids in foods into the circulating plasma NEFA accompanies a similar daily flow from adipose, ensuring continual mixing of the supply of essential nutrients to tissues.

In contrast to the linear accumulation of dietary EFA into triglycerides, the n-3 and n-6 18-carbon EFA led to accumulated elongation and desaturation derivatives in liver 20- and 22-carbon HUFA, which had a competitive, hyperbolic relationship to the dietary supply (Mohrhauer and Holman 1963a, 1963b). Detailed quantitative reports showed that small

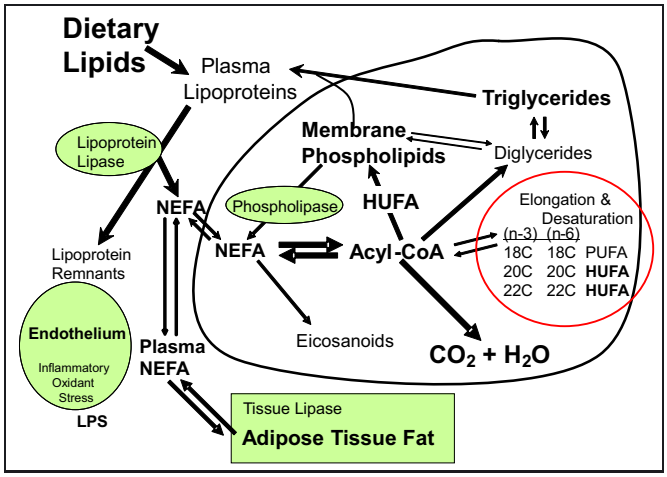


Fig. 1. Flow of essential fatty acids through the plasma NEFA pool. Dietary fats enter plasma as triglycerides in chylomicron particles released from the intestine. Hydrolysis by lipoprotein lipase releases NEFA that mix with NEFA released from adipose tissue and with NEFA hydrolyzed from the very low density lipoprotein secreted by the liver. The half-life of plasma NEFA is about 2 to 4 min.

amounts of dietary linoleate (18:2 n-6) and linolenate (18:3 n-3) very efficiently maintain in a competitive, hyperbolic manner the balance of n-3 and n-6 HUFA in liver lipids. The diet-tissue relationship for HUFA accumulation in laboratory rats resembled the long-familiar enzymatic relationship: action = $V_{max}/(1+K1/S1(1+S2/K2))$. Values for the apparent mid-points ($K1$ and $K2$) for the impacts of dietary substrates, $S1$ and $S2$, affecting tissue HUFA proportions were near 0.1 percent of food energy (0.1 en%). Thus, in the absence of competing n-3 nutrients, 0.2 en% of the potent n-6 nutrient maintained more than 50% n-6 in HUFA, and a similar outcome occurred with the equally potent n-3 nutrient in the absence of n-6 nutrients.

The impacts of dietary 18:2 and 18:3 on tissue HUFA balance in rats and humans (Lands *et al.*, 1990, 1992) had similar apparent mid-points ($K_{18:2}$ = 0.04 and 0.04, and $K_{18:3}$ = 0.07 and 0.06, respectively). The 18-carbon nutrients were very much more abundant than the 20- and 22-carbon nutrients in the foods eaten by the people studied. Also, intakes of n-6 nutrients were several-fold greater than n-3 nutrients, leading to tissue HUFA balances near 75% n-6 in HUFA. Later studies of urban North Americans reported average values near 80% n-6 in HUFA (Lands, 2008), and a study of 287 American soldiers reported an average value of 81% n-6 in HUFA (Lin *et al.*, 2014).

The competitive, hyperbolic diet-tissue relationship was set into an equation with constants that fit experimental data for rats, mice and humans. Using the measured wt% of linoleate and linolenate in fasting plasma triglycerides to estimate the average en% ingested allowed the observed % n-6 in HUFA to give a successful prediction of the different number of capsules of omega-3 supplement taken by individuals in a "blinded" clinical research study (Lands *et al.*, 1992). To demonstrate the applicability of the equation to populations that eat significant amounts of n-3 HUFA, the equation fit results from two different groups of Japanese whose average voluntary food intakes gave predicted and observed HUFA

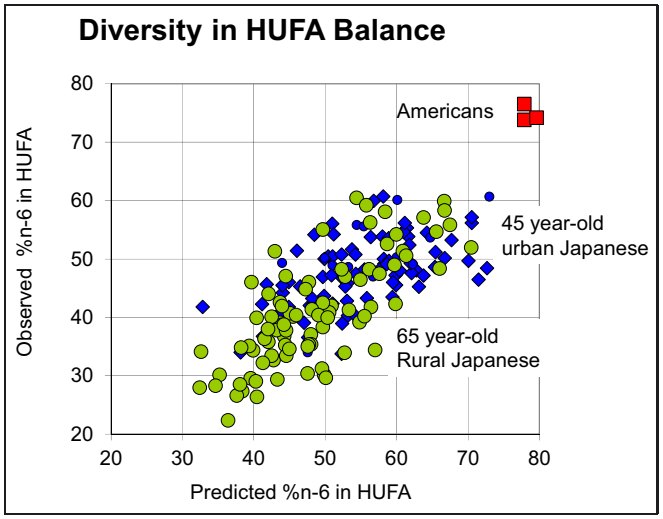


Fig. 2. The diet-tissue equation predicts outcomes for a wide variety of EFA intakes. Detailed diet assessments for Japanese and American volunteers gave predicted % n-6 in HUFA values that agreed with observed gas chromatographic analyses. The figure published by Lands, W.E.M. (2003).

balances ranging from 30 to 60% n-6 in HUFA (Lands, 2003). Figure 2 shows how the Japanese EFA intakes differed from those for typical American food choices which give predicted and observed HUFA balances near 70 to 80% n-6 in HUFA.

The predictive equation (http://www.efaeducation.org/hufacalc.html) was embedded into a simple spreadsheet (http://www.efaeducation.org/dietbalance.html) to help design clinical nutrition interventions that could generate the intended HUFA balances. It also successfully predicted impacts of n-3 and n-6 nutrients on tissue HUFA balance for data from 34 different published studies of nearly 4000 people in 92 groups from 11 different countries (Strandjord *et al.*, submitted). While providing early evidence that the % n-6 in HUFA is a useful biomarker for interpreting the impact of dietary n-3 and n-6 EFA on HUFA balance, the report noted that the % n-6 in HUFA for different ethnic groups related to the incidence of cardiovascular deaths in those groups (Lands *et al.*, 1992), making the biomarker useful for health risk assessment as well as nutrient intake assessment.

An illustration of how the HUFA balance helps interpret epidemiological data came from some paradoxical aspects of the Nurses' Health Study when relating dietary EFA intakes to health outcomes. This large longitudinal study found no statistically significant association of depression with low intakes of n-3 nutrients for 54 632 American women (Lucas *et al.*, 2011), whereas a cross-national association had earlier reported a strong relationship (Hibbeln *et al.*, 2006). The data in Table 1 show dietary intakes in milligrams per day (mg/d) of four types of EFA recorded for people grouped by different quintiles of intake of either the 18-carbon n-3 nutrient or the 20- and 22-carbon n-3 HUFA nutrients. The diet-HUFA equation combines these four types of EFA to predict the likely % n-6 in HUFA that is associated with the two different sets of quintiles.

For higher quintiles of n-3 alpha-linolenate (ALA; 18:3 n-3) intake, there was a paradoxical progressively higher predicted % n-6 in HUFA. This was due to the typical American food sources of 18:3 n-3 having even greater amounts of 18:2 n-6. The situation illustrates a serious limitation when neglecting the balance between the n-3 and n-6 nutrients that jointly affect tissue HUFA balance and using only one of two types to interpret health status. The alternative set of quintiles based on dietary n-3 HUFA intakes had an expected progressively lower predicted % n-6 in HUFA with greater n-3 HUFA intake. However, even though mean intakes of n-3 HUFA ranged several-fold from 70 to 410 mg/d, the much greater intakes of n-6 nutrients kept the predicted biomarker values near 71 ± 4% n-6 in HUFA. Again, assessing the impact of n-3 nutrients while neglecting the accompanying n-6 nutrients, gives an incomplete and misleading view of the competitive metabolic situation. While a numerical statistical significance for the different quintiles for 54 632 women is evident, the biological significance of varying the % n-6 in HUFA by a percentage point or two is not. The cross-national association that showed a strong relationship with clinical conditions involved a biologically significant difference in biomarker values that ranged from 40% to 80% n-6 in HUFA (Hibbeln *et al.*, 2006). That biologically significant difference in HUFA balance provided very different proportions of competing eicosanoid precursors which have an important role in health.

3 Different n-3 and n-6 HUFA proportions in health risk assessment

Stimulating cytosolic phospholipase A2 activity in tissues releases highly unsaturated fatty acids (HUFA), which act as n-3 and n-6 substrates for cyclooxygenases that form prostaglandins and for lipoxygenases that form leukotrienes. Cycloxygenase action is much more rapid with n-6 than n-3 HUFA, and many prostaglandin receptors respond more vigorously with n-6 than n-3 prostanoids (Wada *et al.*, 2007). Similarly, LTC synthase forms cysteinyl leukotrienes much more rapidly with n-6 than n-3 LTA, and the BLT receptor responds 50-fold more vigorously with n-6 LTB4 than n-3 LTB5 (Lands, 2014). The vigorous actions of n-6 eicosanoids can shift healthy physiology toward pathophysiology for people who have high proportions of n-6 arachidonate in tissue HUFA. As a result, the % n-6 in HUFA is a useful biomarker for health risk assessment, and the diet habits that cause the value to be greater than 50% are important causal mediators to be managed with preventive nutrition.

Groups whose average food choices maintained HUFA balances above 50% n-6 in HUFA had a greater risk of heart attack death than those with values below 50% (Lands, 2003). Similarly, groups with HUFA balances above 70% n-6 in HUFA had higher annual healthcare claim costs than those with HUFA balances near 60% (Lands, 2011). The higher expenses likely reflect the large number of health conditions with excessive n-6 eicosanoid actions which are listed among the top 25 most prevalent health conditions (Loeppke *et al.*, 2009). When a randomized controlled clinical trial had patients lower their intake of omega-6 nutrients and increase their intake of omega-3 nutrients for three months, the average health risk assessment value shifted from 77 to 63% n-6 in HUFA, and the

Table 1. Evaluating quintiles of essential fatty acid intake for health risk assessment. Data on intakes of the four types of essential fatty acid are from Lucas *et al.*, 2011. The related % n-6 in HUFA was estimated using the 2002 predictive equation.

	Nurses' health study (n = 54 632)									
	ALA intake quintiles					n-3HUFA intake quintiles				
mg/d 18:3 n-3 ≫	730	860	940	1040	1240	950	960	960	960	970
mg/d 18:2 n-6 ≫	7500	8300	9000	9500	10 900	9200	9200	9100	9000	8800
mg/d n-3 HUFA ≫	210	210	210	210	210	70	130	180	250	410
mg/d n-6 HUFA ≫	130	130	130	130	140	110	120	130	140	160
est %n-6 in HUFA =	69	70	71	71	73	76	74	72	70	65
			71 average	2 stdev				71 average	4 stdev	

Data from Table 1 – Lucas *et al.*, 2011. *Am. J. Clin. Nutr.* 93: 1337–1343.

patients had 40% less clinical events and needed 40% less medication (Ramsden *et al.*, 2013).

In the absence of n-3 nutrients, values for the biomarker above 50% n-6 in HUFA are associated with an adequate supply of EFA and are attained by linoleate intakes near 0.2 en%. However, the examples above show that chronic HUFA balance values above 50% n-6 in HUFA are associated with many health disorders. Thus, dietary n-6 linoleic has a very narrow therapeutic window near 0.1 to 0.3 en% which, fortunately, can be widened by dietary n-3 nutrients (Lands, 2014). An expert panel reviewing evidence for the Department of Defense concluded that "based on studies analyzing omega-3 and omega-6 fatty acid balance, it would be unethical to not attempt elevating the omega-3 status among U.S. military personnel" (Coulter, 2014).

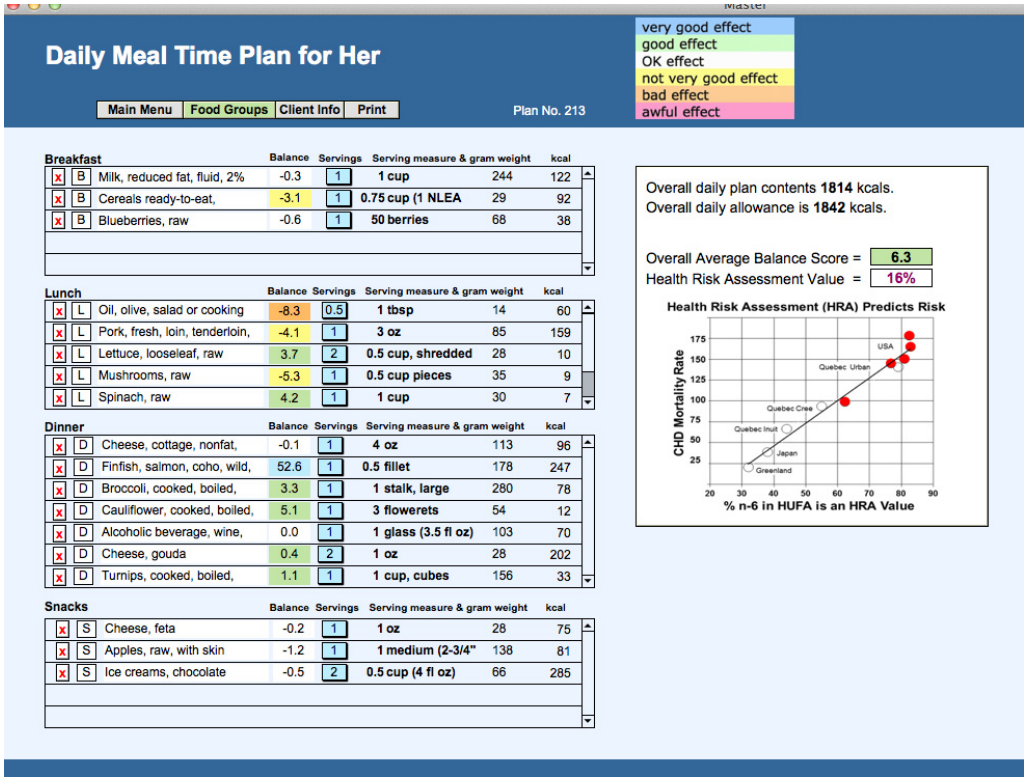
4 Choosing foods to balance competing n-3 and n-6 HUFA

To easily recognize and choose foods that will shift tissue HUFA balance in a desired direction, the Omega 3-6 Balance Score compresses USDA Nutrient Database data on the mg per kcal of eleven different n-3 and n-6 EFA in a food item (http://www.nal.usda.gov/fnic/foodcomp/search/), expressing them as a single quantitative value (Lands & Lamoreaux, 2012). The scores range from –100 to +200, and they relate directly to the associated health risk assessment value of % n-6 in HUFA. Foods with positive scores increase the % n-3 in HUFA, and foods with negative scores increase the % n-6 in HUFA. Traditional food habits have average Omega 3-6 Balance Scores near +3 for Inuit, +1 for Japanese, –4 for Mediterranean and –6.5 for American people. These average food scores correspond to health risk assessment values near 30%, 45%, 62% and 78% n-6 in HUFA, respectively.

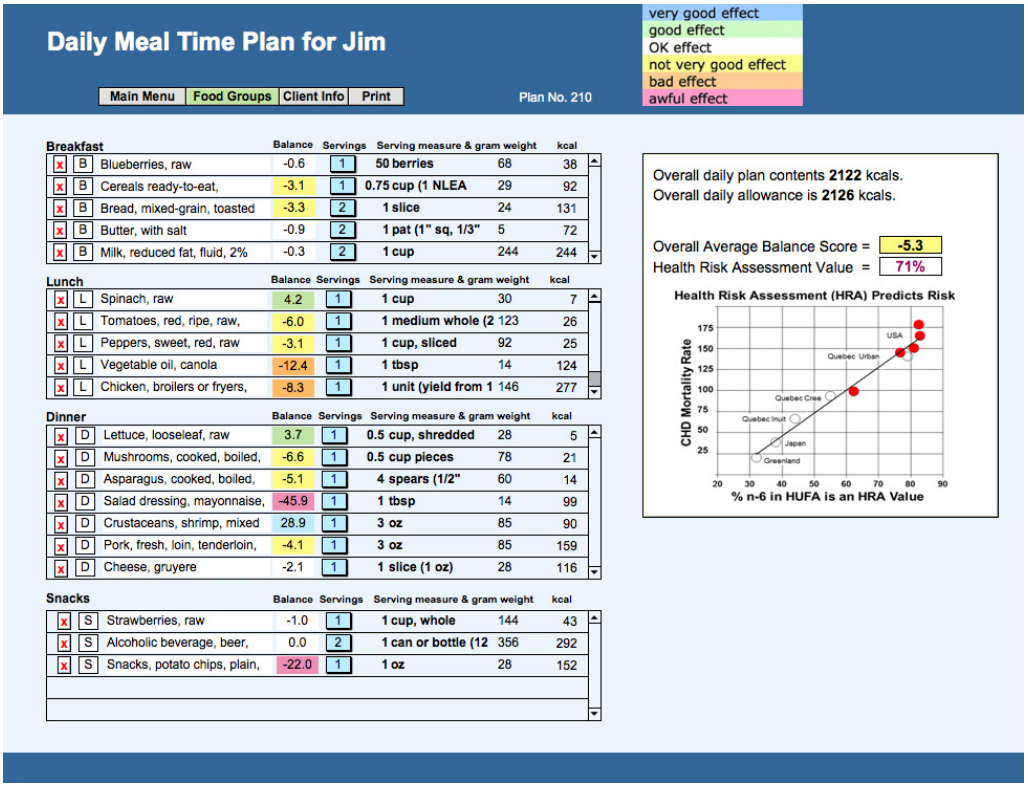
The USDA list of the top 100 American food items (Haytowitz, 2012) has an average balance score of –6.2. The list contains no seafood with large positive scores (*e.g.*, salmon, +62; herring, +70, mackerel, +57). Removing ten items with the most negative scores (*e.g.*, soybean oil, –50; mayonnaise, –46; tub margarine, –39; peanut butter, –24) gives a list of 90 foods with an average balance score near –4, similar to that for traditional Mediterranean diets. The four items with very negative scores noted above illustrate food items that are gradually being added to daily foods in Mediterranean countries where blood samples are showing steadily higher values for % n-6 in HUFA. Although hundreds of vegetables like cabbage, potatoes and onions have scores near 0, the scores for prepared foods are often much more negative; coleslaw (–14 to –33), potato salad (–21), potato chips (–33), fried onion rings (–11).

Table 2 shows some common staple foods that humans have eaten for centuries. Interestingly, the staples of tropical central and west Africa have values near 0, and may reflect foods consumed during the early stages of hominid evolution. About 10 000 years ago, humans began to cultivate grains, which have Omega 3-6 Balance Scores near –4 (except for rice; –0.3). Only in the second half of the 20th century did people in "modern Western" countries begin to consume large quantities of vegetable oils with very negative scores (Blasbalg *et al.*, 2011). This trend in "modern Western" diets has now spread to Mediterranean and Japanese communities. Most staples became familiar foods long before society was aware of the existence of essential fatty acids and the potent mediators that they form. It seems likely that the rapid increase in average consumption of n-6 nutrients has produced unintended, unexpected and undesired consequences on human health.

To avoid offering ambiguous vague advice about eating "healthy meals" and to help people make explicit informed choices of specific daily foods, a simple "app", Omega Foods, was developed. It lists Omega 3-6 Balance Scores of over 5000 foods (http://www.efaeducation.org/Omega3-6BalanceApp.html) and can be downloaded to computers and mobile devices. The scores provide explicit nutrient balances in food items to use when planning meals, shopping or talking about foods with friends. The scores were further incorporated into a personalized daily menu planning computer program, Omega Meals, to help people avoid two major preventable nutrition imbalances that cause many unwanted health conditions: 1 – imbalanced intakes of n-3 and n-6 nutrients; 2 – imbalanced intake and expenditure of food energy. The Omega Meals program helps the user assemble explicit food combinations that fit their personal tastes, lifestyle characteristics and health risk assessment goals (http://www.efaeducation.org/Omega3-6BalanceApp.html). The program's database includes illustrative menu plans with predicted health risk assessment value outcomes between 15% and 88% n-6 in HUFA. Figure 3 illustrates how two different combinations of familiar foods can give daily meal plans with health risk assessment values of either 16% or 71% n-6 in HUFA.



(a)



(b)

Fig. 3. The Omega Meals software program combines diverse food choices to meet individual personal tastes, lifestyles and health risk assessment goals. (a) A 1814 kcal plan with over 18 different food items with a predicted HRA outcome of 16% n-6 in HUFA. (b) A 2122 kcal daily plan with over 20 different food items with a predicted HRA outcome of 71% n-6 in HUFA.

Table 2. Composition of major staple foods.

Staple food	Annual production	Protein	Carbo-hydrate	Fat	Omega 3-6 balance score	
	Million tons	(%)	(%)	(%)		
Tropical foods						
cassava	233 Mt	1.4	38	0.3	–0.1	
sweet potato	110 Mt	1.6	20	0.1	–0.5	
yam	52 Mt	1.5	28	0.2	–0.4	
plantain	34 Mt	1.3	32	0.4	–0.1	
taro	7 Mt	0.5	26	0.1	–3	
Grains						
corn, maize	823 Mt	9.4	76	4.7	–3	oil, –59
rice, white	690 Mt	7.1	79	0.7	–0.3	oil, –36
wheat	685 Mt	12.6	71	1.5	–2	oil, –54
sorghum	66 Mt	11.3	79	3.3	–4	
millet	30 Mt	11	73	4.2	–5	
oats	24 Mt	17	66	6.9	–6	
Legumes						
soybeans	231 Mt	36	30	20	–17	oil, –59
peanuts	45 Mt	26	16	49	–29	oil, –36
beans	23 Mt	22	62	1.4	–0.3	
peas	11 Mt	24	64	1.2	–1	

A useful concept for informed preventive nutrition in wellness programs is to NIX the 6 while you EAT the 3.

5 Summary

While treatment medicine acts to lower signs and symptoms of an individual's recognized disorders, preventive nutrition acts to identify and avoid explicit nutrient imbalances that cause an individual's need for medical treatments. For existing scientific evidence to help build effective ways to diminish harmful human health conditions, we must set it in the context of health beliefs by which individuals decide to take action. Actions come from an awareness and belief of personal likelihood of harm from the condition, and the health risk assessment biomarker, % n-6 in HUFA, easily indicates each individual's relative imbalance in eicosanoid precursors. Awareness and belief of widespread n-6 eicosanoid-based causes of harm has been extensively developed during 50 years of research and development of a wide set of effective pharmaceutical products that lower excessive n-6 eicosanoid actions. Awareness and belief of the explicit contribution that each food item consumed makes to the causal health risk assessment factor, % n-6 in HUFA, is aided by user-friendly tools which facilitate personal food choices to balance eicosanoid precursors and improve health conditions. Importantly, freely available Omega Foods and Omega Meals programs easily inform individuals of the likely impact of each food item they choose to eat. Each person will act on their own personal awareness and belief as they consider preventing a widespread preventable nutrient imbalance that causes a need for treatments.

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