Healthy intakes of n−3 and n−6 fatty acids: estimations considering worldwide diversity[1–5]

Joseph R Hibbeln, Levi RG Nieminen, Tanya L Blasbalg, Jessica A Riggs, and William EM Lands

ABSTRACT

Background: The worldwide diversity of dietary intakes of n−6 and n−3 fatty acids influences tissue compositions of n−3 long-chain fatty acids (LCFAs: eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids) and risks of cardiovascular and mental illnesses.

Objective: We aimed to estimate healthy dietary allowances for n−3 LCFAs that would meet the nutrient requirements of 97–98% of the population.

Design: Deficiency in n−3 LCFAs was defined as attributable risk from 13 morbidity and mortality outcomes, including all causes, coronary heart disease, stroke, cardiovascular disease, homicide, bipolar disorder, and major and postpartum depressions. Dietary availability of n−3 LCFAs from commodities for 38 countries and tissue composition data were correlated by best fit to each illness in deficiency risk models.

Results: The potential attributable burden of disease ranged from 20.8% (all-cause mortality in men) to 99.9% (bipolar disorder). n−3 LCFA intake for Japan (0.37% of energy, or 750 mg/d) met criteria for uniformly protecting >98% of the populations worldwide. n−3 LCFA intakes needed to meet a tissue target representative of Japan (60% n−3 in LCFA) ranged from 278 mg/d (Philippines, with intakes of 0.8% of energy as linoleate, 0.08% of energy as α-linolenate, and 0.06% of energy as arachidonic acid) to 3667 mg/d (United States, with 8.91% of energy as linoleate, 1.06% of energy as α-linolenate, and 0.08% of energy as arachidonic acid).

Conclusions: With caveats inherent for ecologic, nutrient disappearance analyses, a healthy dietary allowance for n−3 LCFAs for current US diets was estimated at 3.5 g/d for a 2000-kcal diet. This allowance for n−3 LCFAs can likely be reduced to one-tenth of that amount by consuming fewer n−6 fats. *Am J Clin Nutr* 2006; 83(suppl):1483S–93S.

KEY WORDS n−3 Fatty acids, Dietary Reference Intake, Adequate Intake, Recommended Dietary Allowance, docosahexaenoic acid, eicosapentaenoic acid, arachidonic acid, linoleic acid, dose-response study, omega-3 fatty acids

INTRODUCTION

The charge of this conference was to consider factors relevant to estimating healthy intakes of the n−3 long-chain fatty acids (LCFAs) with special consideration of the role of the 18-carbon fatty acids α-linolenate (α-LNA) and linoleate (LA), which are precursors for the n−3 LCFAs and the n−6 LCFAs [predominantly arachidonic acid (AA)], respectively. n−3 LCFAs are 20- and 22-carbon fatty acids, operationally defined here as the sum of eicosapentaenoic acid (20:5n−3, or EPA), docosapentaenoic acid (22:5n−3, or DPA), and docosahexaenoic acid (226:n−3, or DHA). In recent years, n−3 LCFAs have been specifically recommended for the secondary prevention of cardiovascular disease (1) and are the focus of considerable attention for the prevention and treatment of disorders with an inflammatory component, including type 2 diabetes, irritable bowel syndrome, macular degeneration, rheumatoid arthritis, asthma, several cancers, and psychiatric disorders (2–8). These illnesses represent significant burdens of disease around the world.

The process of determining a recommendation is too complex to be considered here, but 3 criteria served as useful endpoints in estimating healthy intakes: the percentage of the population protected, the reduction in chronic disease, and the consideration of tissue compositions. For example, a Recommended Dietary Allowance functions as a subgroup of the Dietary Reference Intake and is defined as the "average daily nutrient intake level sufficient to meet the nutrient requirement of nearly all (97–98%) healthy individuals in a particular life stage and sex group" (9, 10). In the past, the idea of a "nutrient requirement" was linked to the concept of "essentiality," and dietary allowances were developed with the goal of preventing signs or symptoms of deficiency. In the relatively new guidelines for Dietary Reference Intakes, the Institute of Medicine requires that "reduction in the risk of chronic degenerative disease [be] included in the formulation of the recommendation rather than just the absence of signs of deficiency" (9, 10). To meet the definition for reducing chronic diseases, the nutrient requirement for n−3 LCFAs was characterized as decreasing the risk of morbidity and mortality for n−3 LCFA-related chronic illnesses rather than simply preventing scaly dermatitis or skin atrophy, as is the case for LA.

[1] From the Laboratory of Membrane Biochemistry and Biophysics and the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD.

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[5] Address reprint requests to JR Hibbeln, Senior Clinical Investigator, LMBB, National Institute on Alcohol Abuse and Alcoholism, NIH, 31 Center Drive 1B58 MSC2088, Bethesda, MD 20892-2088. E-mail: jhibbeln@mail.nih.gov.

This analysis focuses on cardiovascular disease mortality and the prevalence of mental illness in our estimation of healthy dietary intakes of n−3 LCFAs for 3 reasons. First, recent reviews of evidence-based medicine link deficient intakes of n−3 LCFAs with increased risk of cardiovascular disease and stroke (2–8), and a compelling, but still emerging body of data indicates efficacy in psychiatric illnesses. Second, comparable data are available regarding current human diversity of both apparent dietary intakes (11) and risks of morbidity and mortality for use in international ecologic analyses. Mortality data were available from a single source, World Health Organization age-adjusted surveillance data (12), and for each psychiatric illness, morbidity or mortality data were available from prior publications by one of the authors (JRH) (13–16). Third, mechanistic links between n−3 LCFA deficiencies and increased risks of illness are biologically plausible (13, 14).

Dose-response deficiency models were constructed for our analysis by using ecologic data from 38 countries with a target of identifying a representative population with a reduction of 98% in all risks potentially attributable to deficient intakes of n−3 LCFAs. However, tissue compositions of n−3 LCFAs are closer determinants of risk than are unadjusted dietary intakes. World diversity of tissue LCFA composition predicts world diversity of cardiovascular mortality (17). Concurrent intakes of α-LNA, the precursor for n−3 LCFAs, and of the n−6 fatty acids LA and AA were considered, because these essential fatty acids all influence tissue proportions of n−3 fatty acids in LCFAs (18–21).

MATERIALS AND METHODS

Ecologic dose-response models

Commodities data for the domestic supply of foods available for human consumption, or disappearance data, expressed as metric tons $\cdot$ capita^{-1} $\cdot$ d^{-1}, were available for 1995 for 38 countries from the statistical services of the Food and Agriculture Organization (FAO-STAT) of the World Health Organization (11). FAO-STAT categories included poultry meats, pig meats, eggs, bovine meats, goat and mutton, crustaceans, demersal fish, freshwater fish, marine fish, pelagic fish, mollusks, coconut oil, cottonseed oil, groundnut, maize germ oil, olive oil, palm oil, palm kernel oil, rape or mustard oil, rice bran oil, sesame oil, soybean oil, and sunflower oil. These food categories were chosen because the aggregate of meat, eggs, and seafood has been shown to account for 97% of all n−3 LCFA dietary intake, and seed oils are the dominant sources of LA and α-LNA (22, 23).

The essential fatty acid compositions of foods representative of each commodities category (**Table 1**) were estimated from the US Department of Agriculture food-composition database version 17 (24), except for several commodities with reported n−3 LCFA composition values for specific foods that better represented the world diversity of food composition (25–27). Disappearance data for each food category were then converted to gross availability, or "available intake," for each essential fatty acid in each commodity category by using our estimated food source composition values (eg, mg n−3 LCFA/100 g food source). The disappearance of the total milligram quantities of each fatty acid was summed from all commodities and then converted to energy (9 kcal/g). The contribution of each fatty acid was expressed as a percentage of energy available from disappearance of total calories from all commodities to adjust for differences between disappearance and actual consumption. In Table 1, estimations for pig, bovine, goat and mutton, and poultry were calculated by using weighted averages of shown food samples to derive the fatty acid composition of meat with equal parts untrimmed cuts and lean-portion-only cuts. Poultry meats were the average of 4 poultry samples. Pig meats were the average of pork loin without fat from 2 sources and composite pork with fat (weighted twice). n−3 LCFAs for bovine meats were estimated as the average of 6 lean samples and 1 US Department of Agriculture sample including fat (weighted 6 times). Goat and mutton was the average of lamb food samples plus the average of goat food samples divided by 2. Freshwater fish was the average of freshwater bass (weighted twice) and rainbow trout. Demersal fish was the average of flatfish and halibut. Pelagic fish was the average of tuna, salmon, cod, and pollock. Marine fish (other) was an average of the derived values for mollusks, crustaceans, pelagic, demersal, and freshwater fish. These estimations assumed uniform discrepancies between nutrients available for dietary intake and actual ingestion for all foods, ie. the waste of meat or fat calories due to spoilage, trimming, discarding, or other causes was similar for seed oils, seafood, and other foods.

Age-adjusted mortality due to cardiovascular disease, coronary heart disease (CHD), stroke, and all-cause mortality for both men and women for 1995, or the closest available year, from World Health Organization annual mortality data were used (12, 28). Previously published rates of homicide mortality (14) and prevalence rates of postpartum depression (15), major depressive disorder (13), and bipolar disorder (16) in comparison with the seafood disappearance data were used with methods previously reported.

Statistical analysis

Twelve independent comparisons of available dietary n−3 LCFA percentages of energy with disease outcomes across countries were assessed for best linear and nonlinear relation by using iterative curve fitting regression analyses with SIGMA PLOT (version 8.0; SPSS Inc, Chicago, IL). Linear, exponential decay, power, and logarithmic models were each examined with positive and negative slopes. Data were examined for normality of distribution and residuals. In addition to the 12 models of dietary available intake with risk, a correlation comparing lower percentages of n−3 fatty acids in tissue LCFAs to greater cardiovascular mortality was generated from previously published data (19, 29) by using the following relation (17):

$$\%\ \text{of n}-3\ \text{fatty acids in LCFAs} = 100 - \%\ \text{of n}-6\ \text{fatty acids in LCFAs} \quad (1)$$

in which *LCFA* substituted for highly unsaturated fatty acids (HUFA).

Estimation of morbidity and mortality attributable to deficiencies of n−3 LCFAs

The asymptote for each dose-response curve was operationally defined as the available intake of n−3 LCFAs (as a percent of energy) associated with no further decreased risk of illness. To avoid extrapolation beyond the available data, the asymptote also operationally defined the *y* value occurring at the intersection of the dose-response curve and the highest subpopulation mean available intake of n−3 LCFAs. In most cases, this corresponded

TABLE 1
Estimated fatty acid composition of food commodities by category[1]

	n−6 Fatty acids		n−3 Fatty acids			
Commodities[2]	LA (18:2n−6)	AA (20:4n−6)	LNA (18:3n−3)	EPA (20:5n−3)	DPA (22:5n−3)	DHA (22:6n−3)
	mg/100 g			*mg/100 g*		
Poultry meats[3]	1443	98	73	5	18	25
Chicken, with skin (05006)[4,5]	2880	80	140	10	10	30
Chicken, without skin (05011)[4]	550	80	20	10	20	30
Turkey with skin (05165)[4]	1700	110	110	0	20	20
Turkey, without skin (05167)[4]	640	120	20	0	20	20
Pig meats[3]	831	68	53	3	7	2
Pork loin, without fat[4]	262	53	12	3	7	2
Pork loin, without fat (10040)[4]	440	60	20	NA	NA	NA
Pork, with fat (10187)[4]	1310	80	90	NA	NA	NA
Eggs[3]	1272	156	31	0	6	44
Bovine meats[3]	277	24	105	5	8	4
Beef rib eye[4]	178	46	10	5	12	2
Beef rib eye (13098)[4]	240	20	10	NA	NA	NA
Beef sirloin[4]	94	9	20	5	15	10
Beef Swiss steak[4]	182	18	61	9	0	8
Nelore *longissimus dorsi*[4]	115	11	15	3	9	2
Canchim *longissimus dorsi*[4]	101	9	13	4	5	2
Beefalo *longissimus dorsi*[4]	98	9	16	3	6	2
Beef, with fat (13795)[4]	410	30	190	NA	NA	NA
Goat and mutton[3]	460	64	178	5	19	21
Lamb loin chop[4]	369	84	54	5	7	10
Lamb steak leg[4]	202	12	126	14	68	84
Lamb raw feet[4]	198	66	27	0	6	9
Lamb, Australian (17280)[4]	422	69	202	NA	NA	NA
Lamb, New Zealand (17062)[4]	550	10	420	NA	NA	NA
Lamb, domestic (17226)[4]	1090	70	330	NA	NA	NA
Goat shoulder[4]	337	109	44	9	10	5
Goat leg[4]	262	65	49	0	11	9
Goat (17168)[4]	100	60	20	NA	NA	NA
Freshwater fish[3]	295	104	93	245	56	461
Trout, rainbow (15240)[4]	710	25	58	260	0	668
Bass, freshwater (15003)[4]	87	144	111	238	84	357
Demersal fish[3]	19	89	37	82	70	199
Flatfish, flounder and sole (15028)[4]	8	38	8	93	46	106
Halibut (15036)[4]	30	139	65	71	94	292
Pelagic fish[3]	60	90	74	185	111	619
Tuna, bluefin (15117)[4]	53	43	0	283	125	890
Salmon, Atlantic (15076)[4]	172	267	295	321	287	1115
Cod, Atlantic (15015)[4]	5	22	1	64	10	120
Pollock, Atlantic (15065)[4]	9	26	0	71	22	350
Crustaceans, shrimp (15149)[3]	28	87	14	258	46	222
Mollusks, mussel (15164)[3]	18	70	20	188	22	253
Marine fish, other[3]	31	84	36	178	62	323
Coconut vegetable oil (04047)[3]	1800	0	0	0	0	0
Cottonseed vegetable oil (04502)[3]	51 500	100	200	0	0	0
Groundnut oil[3]	32 000	0	0	0	0	0
Maize germ oil[3]	58 000	0	700	0	0	0
Olive oil[3]	7900	0	600	0	0	0
Palm kernel vegetable oil (04513)[3]	1600	0	0	0	0	0
Palm vegetable oil (04055)[3]	9100	0	200	0	0	0
Canola oil (04582)[3]	20 300	0	9300	0	0	0
Rice bran vegetable oil (04037)[3]	33 400	0	1600	0	0	0
Sesame oil (04058)[3]	41 300	0	300	0	0	0
Soybean oil (04044)[3]	51 000	0	6800	0	0	0
Sunflower vegetable oil (04506)[3]	65 700	0	0	0	0	0

[1] NA, not available.

[2] Estimations of the n−3 and n−6 fatty acid content of commodities were derived by averaging representative food sources from published food-composition tables.

[3] Summary estimated n−3 LCFA compositions.

[4] Domestic supply food categories and representative food sources.

[5] Entries retrieved from the US Department of Agriculture National Nutrient Database for Standard Reference, Release 17, are followed by a 5-digit NDB number in parentheses. All entries were obtained from this database unless otherwise noted in Materials and Methods. Data were not adjusted for country-specific differences in nutrient compositions of foods.

to Icelandic concentrations of 0.43% of energy as n−3 LCFAs, except for the major depression model, for which the furthest point was 0.374% of energy (Japan). The area below the operationally defined asymptote was regarded as the baseline rate of disease that persisted regardless of further increases in intake of n−3 LCFAs. Integral calculus was used to calculate all areas under the curves (Maths Helper Plus; Teachers' Choice Software, Goodna Queensland, Australia). Morbidity or mortality attributable to n−3 LCFA deficiency was defined as the area above the baseline rate of illness, but below the fitted curve, between available intakes of zero and maximal available intakes of n−3 LCFAs and also expressed as a percentage of potentially attributable disease burden.

The efficacy of 3 possible healthy allowances of n−3 LCFAs (0.08% of energy or 180 mg/d, 0.22% of energy or 500 mg/d, and 0.34% of energy or 750 mg/d) was assessed by using integral calculus to determine the areas between the curve and the asymptote, with each of the possible Recommended Dietary Allowances as right boundaries in 3 different scenarios (illustrated in Figure 2 by areas χ, β, and α). These boundary values defined the percentage of the population potentially protected from each disease outcome for each choice. Four factors (dietary availabilities of LA, α-LNA, AA, and EPA + DPA + DHA as a percent of energy) were used as input functions to estimate the percentage of n−3 LCFA in tissues by using a formula empirically derived from human and animal data with modified constants (19, 29). The dietary percentage of energy of n−3 LCFAs needed to maintain n−3 LCFAs in tissue comparable with concentrations in Japan was calculated for 13 countries representing the worldwide diversity of LA in diets (which ranged from <0.89% of energy to nearly 9% of energy). Conversion of required amounts from % of energy to mg n−3 LCFA/d was based on a 2000-kcal/d diet.

RESULTS

Major sources of n−3 LCFAs were fish and seafood, whereas seed oils, eggs, poultry, and pig meat contained the greatest amount of n−6 fatty acids (Table 1). Greater n−3 LCFA availability was inversely related with disease rates in all 12 risk models (**Table 2** and **Figure 1**). Three-factor negative exponential equations provided the best fit for all models, except for major depression, which was a linear fit. These correlations were significant for reduced mortality from stroke for men ($r = -0.59$, $P < 0.002$), stroke for women ($r = -0.57$, $P < 0.004$), CHD for women ($r = -0.45$, $P < 0.04$), cardiovascular disease for men ($r = -0.60$, $P < 0.002$), cardiovascular disease for women ($r = -0.65$, $P < 0.001$), all causes for men ($r = -0.53$, $P < 0.008$), and all causes for women ($r = -0.57$, $P < 0.004$), and for reduced morbidity from postpartum depression ($r = -0.78$, $P < 0.001$), bipolar disorder ($r = -0.86$, $P < 0.002$), and homicide mortality ($r = -0.78$, $P < 0.001$). Additionally, there was a trend for major depression ($r = -0.69$, $P < 0.15$) and CHD for men ($r = -0.38$, $P < 0.1$). Greater n−3 LCFAs in tissue correlated with a lower risk of cardiovascular mortality in a linear regression as previously published ($r^2 = -0.97$, $P < 0.001$) (17).

After subtracting the risk below the asymptote, between 20.8% and 99.9% of disease burdens appeared to be potentially attributable to deficiencies in available intake of n−3 LCFAs (**Table 3**). Rates of illness in Iceland and Greenland were uniformly lower than the projected regression curves, which indicated that further protection was likely to occur with greater n−3 LCFA intake (Figure 1 and **Figure 2**). Evaluation of the 3 possible choices for healthy allowances indicated that available intake at 0.08% of energy prevented enough attributable disease to protect nearly all healthy individuals in only 2 conditions (stroke mortality for men and for women). Available intake at 0.22% of energy did not protect nearly all healthy individuals for CHD mortality for men and for women, total mortality for men and for women, major depression, or bipolar disorder. Available intake at 0.34% of energy was sufficient to reduce risk for ≥98% of the mortality and morbidity in all illness models (Table 3). This level of available intake corresponded with intakes common in Japan. Results of the CHD risk model with tissue composition in Figure 2 also indicate that a tissue composition of 60% of n−3 fatty acids in LCFA, a value common in Japan (30–33), may protect 98.6% of the worldwide risk of cardiovascular mortality potentially attributable to n−3 LCFA deficiency.

The n−3 LCFA intake required to maintain 60% n−3 fatty acids in tissue LCFAs varied 13-fold among nations depending on background essential fatty acid availability (**Table 4**). In general, as concurrent LA availability increased, the estimated requirement for n−3 LCFA intake increased, although intake of α-LNA and AA also played a role. In recognizing that dietary intakes in Mediterranean countries result in a substantial decrease in risk of cardiovascular disease, dietary data are also presented reflecting a tissue goal of 50% n−3 LCFAs, which is nearer to that in Mediterranean countries (Table 4). For Americans consuming a 2000-kcal/d diet, 2178 mg/d (0.98% of energy) may achieve 50% n−3 in tissue LCFA, whereas 3667 mg/d appears necessary to reach a goal of 60% n−3 in LCFA. Lowering LA intake can likely decrease an individual's need for n−3 LCFAs by one-tenth.

DISCUSSION

There was a convergence from 13 dose-response models of n−3 LCFA intake and disease risk on the basis of commodities data for percent of energy as n−3 LCFAs (available dietary intakes) and plasma phospholipid n−3 LCFA composition. These models indicated that the diets and tissue compositions common in Japan meet the nutrient requirements of nearly all the healthy population. Deficiency was defined here as the increased risk of illness attributable to insufficient n−3 LCFA intake. In 12 of 13 independent dose-response models, three-factor negative exponential regression equations provided the best fit between lower available intakes of n−3 LCFAs and greater morbidity and mortality. These models allowed calculation of intakes sufficient to protect 98% of the population from risks of deficiency. Thus, healthy available intakes corresponded with tissue compositions of ≈60% n−3 fatty acids in LCFA (and 40% n−6 fatty acids in LCFA), which has been shown to be associated with low cardiovascular mortality in the Japanese population (30–33).

Japan is a modern industrialized society with a large population and well-documented rates of illnesses and nutrient intakes. Low rates of cardiovascular disease have been consistently reported in Japan, despite high rates of smoking and high blood pressure (34, 35). Thus, we had reasonable confidence in targeting Japanese n−3 LCFA composition as a reliable endpoint. However, because dietary intakes of n−3 LCFAs are not the sole

TABLE 2
Dietary percentages of energy from n−3 long-chain fatty acids (LCFAs) and disease prevalence by country[1]

Country	Dietary n−3 LCFAs	CHD mortality[2]		Stroke mortality[2]		CVD mortality[2]		Total mortality[2]		Homicide mortality[2]	Postpartum depression[3]	Major depression[4]	Bipolar disorder[5]
		M	F	M	F	M	F	M	F				
	% of energy										%	%	%
Bulgaria	0.023	352	132	314	184	938	466	1757	827	10.3	—	—	—
Romania	0.041	388	176	311	208	975	534	1966	967	—	—	—	—
Hungary	0.043	459	169	225	125	899	408	2276	980	7.1	—	—	7.1
Colombia	0.046	190	—	90	—	397	—	—	—	—	—	—	—
Brazil	0.052	—	—	—	—	—	—	—	—	—	24.1	—	—
Argentina	0.053	153	43	133	74	595	260	1383	667	—	—	—	—
Poland	0.066	267	79	111	72	735	325	1722	742	6.1	—	—	—
South Africa	0.069	—	—	—	—	—	—	—	—	—	24.5	—	—
Czech Republic	0.070	391	149	137	82	705	323	1529	717	—	—	—	—
Austria	0.071	223	74	67	41	409	174	995	485	2.4	—	—	—
Germany	0.084	207	72	59	37	375	164	1028	517	2.4	20	5	8.3
Ireland	0.090	367	125	66	46	518	219	1154	649	—	11	—	—
Netherlands	0.091	191	63	51	37	354	148	964	518	2.5	—	—	—
Italy	0.096	150	72	64	26	304	131	953	504	4.5	15.5	—	5.1
Switzerland	0.096	147	41	33	21	273	105	852	423	2.6	10.2	—	6.8
UK	0.103	267	96	57	44	390	180	946	585	2	14.4	—	—
USA	0.103	214	88	43	34	389	192	1054	632	—	11.5	3	4.4
Greece	0.110	176	50	85	56	359	164	877	432	2.3	—	—	—
Australia	0.113	202	73	44	31	298	129	840	466	3.7	18.6	—	—
Israel	0.118	150	65	68	47	287	154	821	532	4.6	12.4	—	5.3
Russia	0.119	737	255	374	231	1310	581	2957	1123	—	—	—	—
France	0.136	92	22	45	23	225	81	991	410	2.2	11	4.5	—
Denmark	0.139	204	76	66	41	360	159	1159	728	—	—	—	—
Sweden	0.139	216	68	51	34	335	132	799	461	2.6	9	—	—
Chile	0.144	—	—	—	—	—	—	—	—	6.2	5.5	—	—
UAE	0.144	—	110	—	84	—	286	1166	748	—	18	—	—
Canada	0.146	200	42	38	40	299	131	894	457	3.7	12.7	5.2	2.2
New Zealand	0.157	287	113	60	44	419	196	994	607	3	17.4	5.8	4.9
Puerto Rico[6]	0.160	185	87	59	31	373	187	1376	632	—	—	3	1.7
China	0.168	100	69	251	170	409	296	1079	716	—	—	0.8	0.8
Spain	0.170	125	34	59	32	267	109	957	398	1.8	13.6	—	—
Portugal	0.203	125	44	144	89	354	177	1186	540	3.1	—	—	—
Korea	0.218	—	—	—	—	—	—	—	—	2.5	—	2.3	1.1
Finland	0.228	340	93	82	50	500	171	1158	494	6.5	—	—	—
Norway	0.244	259	77	55	38	387	146	942	503	2	—	—	1.6
Malaysia	0.341	—	—	—	—	—	—	—	—	—	3	—	—
Japan	0.374	57	20	79	41	186	85	743	341	1.3	2	0.12	—
Iceland	0.435	102	31	26	11	159	57	389	246	0.5	5	—	0.6

[1] CHD, coronary heart disease; CVD, cardiovascular disease; UAE, United Arab Emirates.
[2] Total mortality/100 000 population.
[3] Point prevalence.
[4] Annual prevalence.
[5] Lifetime prevalence.
[6] n−3 LCFA intakes from Jamaica were used as a surrogate for intakes for Puerto Rico.

determinants of tissue n−3 LCFAs, we also considered background intakes of 18-carbon n−3 and n−6 fatty acids and of AA when estimating the dietary intakes of n−3 LCFAs needed to achieve tissue compositions of 60% n−3 LCFAs. We note that the burden of potentially attributable risk for bipolar disorder appears to be unrealistically high (99.9%; *see* Table 3) on the basis of the regression equation generated from data in an original publication (16). Subsequently, additional data reporting a low annual prevalence rate of bipolar disorder in Japan (0.1%) were published (36). Inclusion of these new data did virtually nothing to alter the regression equation or the percentage of potentially attributable disease, which gives greater confidence in this finding. Nonetheless, bipolar disorder is likely due to a multitude of factors, and it is unlikely that 99.9% of bipolar illness is attributable to n−3 LCFA deficiency. To our knowledge, rates of bipolar disorder in Iceland and among Inuits have not been published.

Current recommendations for n−3 LCFA intake are not specified by the Institute of Medicine (10), but have been estimated at 130–260 mg/d (37). Other recommendations range from 200 mg/d in the Netherlands (37) to the American Heart Association's recommendation of 1 g/d for persons with documented CHD (1).

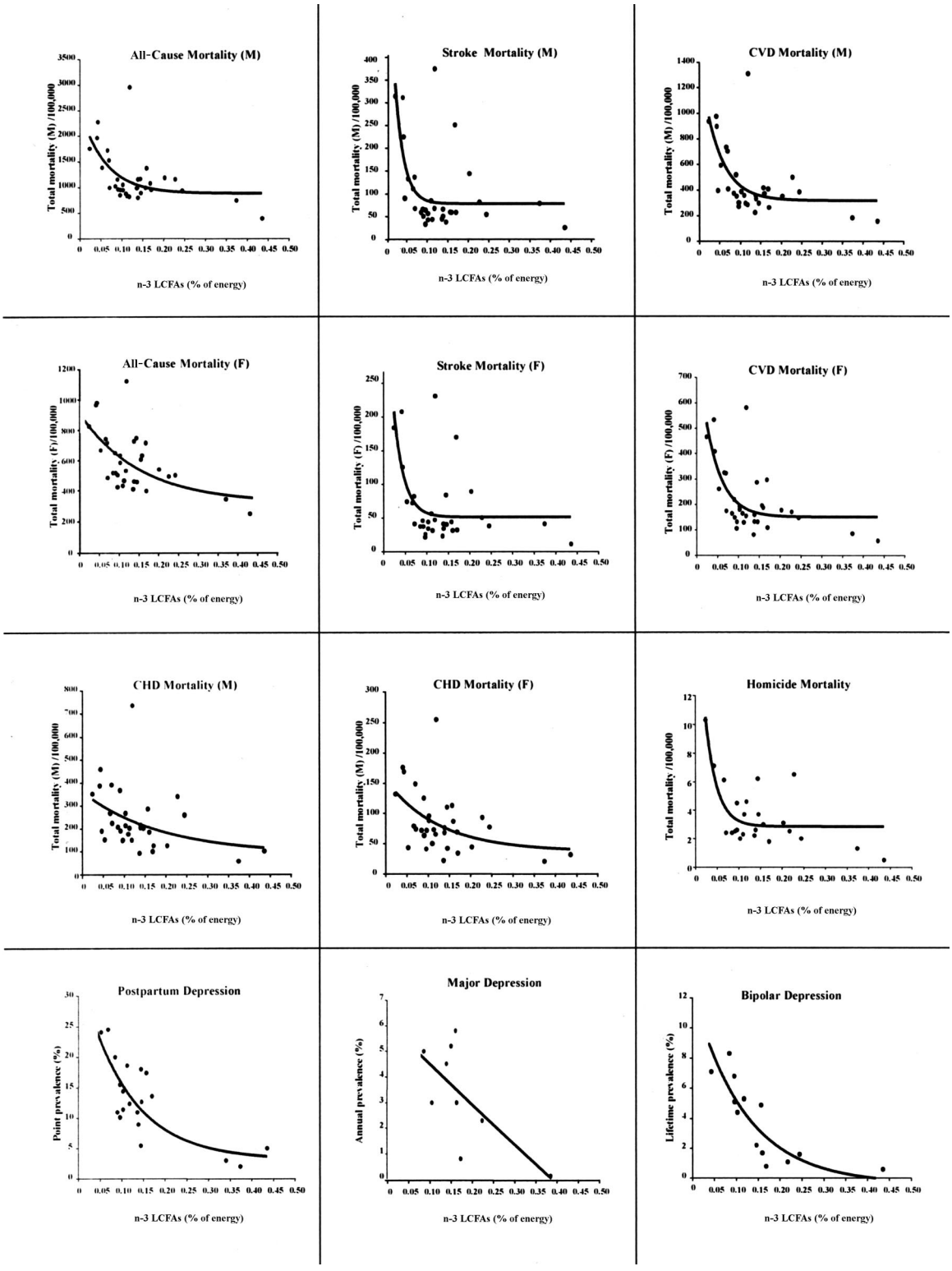

FIGURE 1. Scattergrams by country and best-fit regression curves for ecologic dose-response relations between dietary n−3 long-chain fatty acids (LCFAs) and mortality and morbidity outcomes (*see* Materials and Methods). The dose-response equation was derived by best-fit regression. The asymptote was operationally defined as the n−3 LCFA intake at which disease risk was no longer reduced without projecting past available data. Burden of potentially attributable risk was defined as the ratio of the area above the asymptote over the total area. Population size and differences in age distributions were adjusted for by using the rate of illness (per 100 000) age-adjusted to the European standard distribution. CVD, cardiovascular disease; CHD, coronary heart disease.

TABLE 3
Efficacy of 3 possible dietary intakes in reducing the risk of disease attributable to n−3 long-chain fatty acid (LCFA) deficiency[1]

Disease or disorder model	Disease burden potentially attributable to n−3 LCFA deficiency[3]	Worldwide protection from deficiency at 3 possible intakes of n−3 LCFA[2]		
		0.08% of energy (180 mg/d)[4]	0.22% of energy (500 mg/d)	0.34% of energy (750 mg/d)
	%		%	
CHD mortality, M	41.2	45.2	85.4	97.9
CHD mortality, F	42.5	52.4	89.7	98.6
Stroke mortality, M	32.9	97.7	99.9	>99.9
Stroke mortality, F	31.1	96.4	99.9	>99.9
CVD mortality, M	26.1	83.4	99.3	>99.9
CVD mortality, F	29.1	86.9	99.6	>99.9
Total mortality, M	20.8	73.6	97.7	99.8
Total mortality, F	31.5	48.3	87.3	98.2
Homicide mortality	28.4	95.6	>99.9	>99.9
Postpartum depression	65.5	55.7	91.3	98.9
Major depression[5]	98.5	38.5	83.2	99.2
Bipolar depression[5]	99.9	56.1	92.3	99.5

[1] CHD, coronary heart disease; CVD, cardiovascular disease.
[2] Protection from deficiency was calculated for each possible dietary intake as illustrated in Figure 2 and was repeated for each disease risk relation illustrated in Figure 1.
[3] Percentage of the population disease potentially attributable to deficiency of n−3 LCFAs as illustrated in Figure 2, top panel.
[4] Based on a 2000-kcal/d diet.
[5] These burdens of potentially attributable disease appear high; *see* Discussion.

According to the analysis presented here, these recommendations are inadequate to meet the criteria of a Recommended Dietary Allowance for US and world populations. One exception is the International Society for the Study of Fatty Acids and Lipids recommendation of 500 mg/d, which also includes an adequate intake of LA at 2% of energy and a healthy intake of α-LNA of 0.7% of energy. With the use of an empirical formula (19), this combination translates into a tissue composition of 53% n−3 fatty acids in LCFAs (29, 38). Concurrent dietary intakes of LA, α-LNA, AA, EPA, and DHA should be considered in predicting final tissue proportions of n−3 fatty acids in LCFAs (19). Thus, a healthy dietary allowance for n−3 LCFA intake must be made dependent on concurrent intakes of LA, α-LNA, and AA. A healthy dietary allowance of 3.5 g EPA + DHA/d, which is based on the current per capita background available intake of n−6 fatty acids and α-LNA in the United States, could be reduced to one-tenth of that amount if the intake of n−6 fatty acids, in particular LA, can be lowered to <2% of energy.

A related biomarker of n−3 intake and predicted risk is the omega-3 index (red blood cell EPA + DHA as a percentage of total red blood cell lipids) proposed by Harris and von Schacky (39), for which values >8% are associated with greater decreases in cardiovascular disease risk. This target was based on trials conducted primarily in the United States and does not reflect the worldwide diversity of n−3 and n−6 intakes. In fact, n−6 intake was not considered. For comparison, 60% n−3 fatty acids in LCFAs in tissue is associated with an omega-3 index of ≈12–15%, as seen in Japan. The biomarker target and the target proposed here may seem excessive in comparison with current US dietary habits and other recommendations. However, this allowance can also be regarded as conservative because morbidity and mortality rates for nearly all diseases are even lower for Iceland and Greenland, populations with greater intakes of n−3 LCFAs than in Japan. These countries fell below the dose-response curves generated by the regression analyses, which indicates that greater protection was achieved than was predicted (*see* Figures 1 and 2).

The approach to determining healthy dietary allowances for n−3 LCFAs described here has several unique aspects. To our knowledge, this is the first attempt to set an allowance for n−3 LCFAs that adheres to criteria of meeting the nutrient requirements of nearly all the healthy population. n−3 LCFA deficiency was defined as an increased risk of chronic diseases for which substantial efficacy data exist and for which these nutrients reduce pathophysiologic mechanisms. This ecologic approach took advantage of uniform disappearance data estimating dietary available intakes, compared with direct survey data, which were not available or uniform for every country. The worldwide diversity of available intake of essential fatty acids was also compared with the worldwide diversity of disease burdens to estimate dose-response relations. One additional strength is that both the total n−3 and n−6 dietary availability and resulting tissue profiles from different countries were taken into consideration when determining possible allowances.

There are several obvious weaknesses inherent in comparing countries in these cross-sectional ecologic analyses. These include the lack of adjustment for potential confounding variables; variations in actual compositions of foods; waste that makes food disappearance not equal to intake; differences in diagnostic classifications, especially for psychiatric disorders; and differences in qualities of data collection. The assumption of a uniform composition of meats, eggs, and other food sources across countries is likely confounded by diverse amounts of n−3 LCFAs available to domestic animals; for example, soybean- and corn-fed animals are likely to have very different fatty acid proportions than do grass-fed animals. Thus, the data are not adjusted for country-specific differences in the nutrient compositions of foods. Although intakes are normally expressed specifically for each of 16 life-stage categories, the data necessary to make such

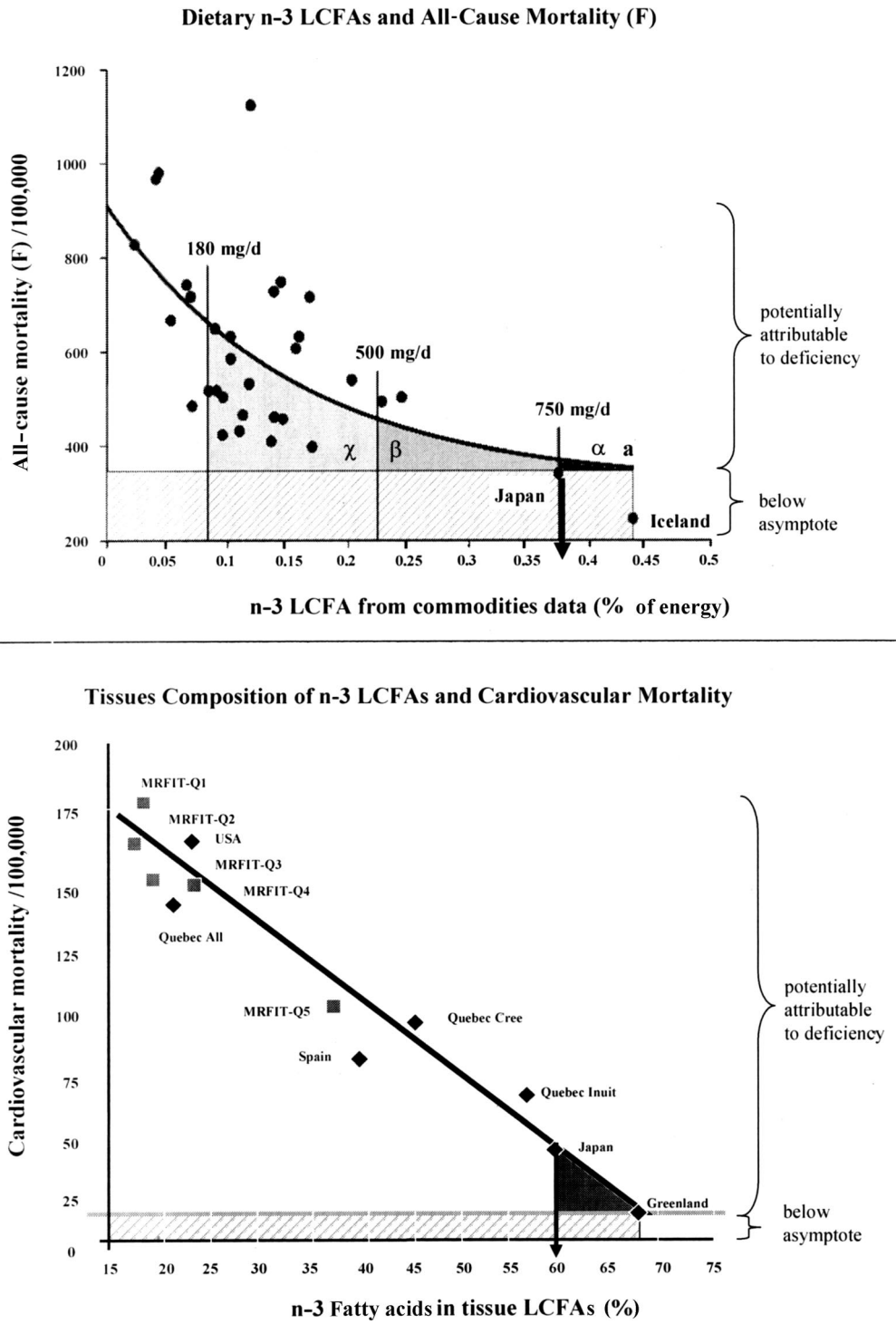

FIGURE 2. Calculation of the disease burden modifiable by n−3 long-chain fatty acids (LCFAs) and testing 3 possible dietary intakes (top panel). Scattergram by country and best-fit regression curve for the ecologic dose-response relation between the percentage of n−3 fatty acids in tissue LCFAs and cardiovascular mortality (bottom). Both dietary intakes and tissue compositions representative of Japan (top and bottom panels) met the criterion of satisfying the nutrient requirements for nearly all the healthy population. Population size and differences in age distributions were adjusted for by using the rate of illness (per 100 000) age-adjusted to the European standard distribution. MRFIT, Multiple Risk Factor Intervention Trial.

inferences were not available in this analysis. The prevalence rates of major depression and CHD were not significantly associated with the disappearance data and thus their contribution should be considered cautiously. Estimation of a healthy intake would preferably have been done with outcome data from large-scale longitudinal intervention trials that each used multiple dose comparisons; assessed several disease outcomes, including cardiovascular and psychiatric morbidity; and monitored tissue

TABLE 4
Dietary n−3 fatty acids required to maintain 2 tissue targets of n−3 long-chain fatty acids (LCFAs): effect of background n−3 and n−6 essential fatty acid intakes in selected countries[1]

Country	Tissue target for n−3 in LCFAs	Concurrent dietary intake			n−3 LCFAs required to meet tissue target
		LA	LNA	AA	
	%		*% of energy/d*		*% of energy (mg/d)*[2]
Philippines	50	0.80	0.08	0.06	0.06 (133)
Denmark	50	2.23	0.33	0.09	0.26 (578)
Iceland	50	2.48	0.33	0.10	0.31 (689)
Colombia	50	3.21	0.24	0.04	0.30 (667)
Ireland	50	3.57	0.42	0.06	0.36 (800)
UK	50	3.91	0.77	0.07	0.39 (867)
Netherlands	50	4.23	0.28	0.08	0.50 (1111)
Australia	50	4.71	0.49	0.07	0.51 (1133)
Italy	50	5.40	0.51	0.06	0.56 (1244)
Germany	50	5.57	0.62	0.06	0.57 (1267)
Bulgaria	50	7.02	0.06	0.05	0.73 (1622)
Israel	50	7.79	0.67	0.07	0.85 (1889)
USA	50	8.91	1.06	0.08	0.98 (2178)
Philippines	60	0.80	0.08	0.06	0.125 (278)
Denmark	60	2.23	0.33	0.09	0.45 (1000)
Iceland	60	2.48	0.33	0.10	0.54 (1200)
Colombia	60	3.21	0.24	0.04	0.51 (1133)
Ireland	60	3.57	0.42	0.06	0.62 (1378)
UK	60	3.91	0.77	0.07	0.72 (1600)
Netherlands	60	4.23	0.28	0.08	0.88 (1956)
Australia	60	4.71	0.49	0.07	0.90 (2000)
Italy	60	5.40	0.51	0.06	0.95 (2111)
Germany	60	5.57	0.62	0.06	1.00 (2222)
Bulgaria	60	7.02	0.06	0.05	1.25 (2778)
Israel	60	7.79	0.67	0.07	1.45 (3222)
USA	60	8.91	1.06	0.08	1.65 (3667)

[1] The target of 60% n−3 fatty acids in tissue LCFAs is illustrated in the bottom panel of Figure 2 and is representative of dietary intakes of Japan, which appear to protect 98% of populations from disease risks (top panel of Figure 2 and all panels of Figure 1). LA, linoleic acid; LNA, α-linolenic acid; AA, arachidonic acid. The target of 50% is presented as an alternative target.

[2] Percent of energy is the proportion of n−3 fatty acids in tissue LCFAs calculated from an equation empirically derived from human and animal data (*see* Subjects and Methods). Values in mg/d are based on a 2000-kcal/d diet.

proportions of LCFAs. Because of cost considerations, relatively few large-scale longitudinal intervention trials have been conducted, let alone as comparisons of multiple doses; thus, this information is not readily available.

It seems likely that a combination of EPA and DHA reflecting nature may be optimally used in dietary supplementation to meet n−3 LCFA intake goals. A major source of dietary n−3 LCFA in our calculations was seafood containing both EPA and DHA in an average ratio of 1:2.3, as calculated from data presented here. High intakes of n−3 LCFAs may be associated with an increased risk of hemorrhagic stroke (31), but this risk may be offset by a decrease in thrombotic stroke and overall stoke mortality. A review of the literature on mental health outcomes shows supplementation with a combination of both EPA and DHA likely to be more effective than use of either alone (40–45). Reports of 50% reductions in depressive symptoms and 37% reductions in felony-level violence (46) in interventional trials are consistent with the large potentially attributable burdens of disease reported in Table 3. However, effect sizes in interventional trials are difficult to compare with these ecologic data, which reflect prenatal and lifetime dietary exposures. In contrast, most intervention trials have, understandably, been conducted over comparatively short periods of time.

This work focuses directly on estimates of the 20- and 22-carbon varieties of n−3 and n−6 essential fatty acids available in membranes, because these are the precursors for the eicosanoids that mediate inflammatory and thrombotic tissue responses (17, 47, 48). The biological availability and activity of n−6 LCFAs, in particular AA, are inversely related to n−3 fatty acids in tissue LCFAs. Greater compositions of EPA, DPA, and DHA in membranes competitively lower the availability of AA for the production of eicosanoids (17, 47, 48). The prevention of the formation of n−6 eicosanoids derived from AA with medications, including cox-2 inhibitors, ibuprofen, acetaminophen, and aspirin, constitutes a substantial proportion of pharmaceutical industry activity. The available tissue composition of AA can be lowered by reducing dietary intakes of the 18-carbon precursor, LA. Conversely, it has been known since the early 1960s that greater dietary intakes of LA increase tissue concentrations of AA, while reducing tissue concentrations of EPA and DHA (20, 49–51). Greater direct intake of preformed EPA and DHA most directly influences greater tissue compositions in comparison with conversion from α-LNA to EPA and DHA, which is poor in humans (21). Thus, recommendations for essential fatty acid intakes focusing only on the 18-carbon fatty acids are subject to substantial variance in tissue proportions of n−3 and n−6 fatty acids in

LCFAs. It is likely that the success and failure of different clinical trials using similar doses of n−3 LCFAs were influenced by differing background intakes of the n−6 fatty acids LA and AA. For example, in the case of the Lyon Diet Heart Study (52), the positive outcomes attributed to α-LNA may be related, in part, to a lower n−6 fatty acid intake, which would enhance conversion of α-LNA to n−3 LCFAs (49, 53). Although LA has been associated with positive health outcomes, including reduced risk of ischemic stroke (54), we are aware of no intervention trials in which LA was actively increased in humans and cardiovascular or psychiatric disease outcomes were measured.

In contrast with considering n−3 fatty acids as a pharmaceutical treatment, Crawford, Cordain, Simolopous, and others (55–57) have advanced the concept of population-wide deficiencies of n−3 LCFAs in modern societies that rely on industrialized agriculture. Those authors cited, in part, that diets during the 4–5 million years of hominid evolution were likely abundant in seafood and other sources of n−3 LCFAs but had sparingly little contribution of calories from n−6-rich seed oils. In stark contrast, at the turn of the recent millennium, a single food source, soybean oil, appears to deliver 20% of all calories in the median US diet, with ≈9% of all calories from linoleic acid alone (58). To our knowledge, inadequate information is available to determine whether it is safe or unsafe to consume 9% of all calories as LA, a precursor to the proinflammatory arachidonic acid. One ecologic study indicated that greater intakes of LA from 1960 to 1999 in each of 5 countries predicted a 100-fold greater risk of homicide mortality (59). The increases in world LA consumption over the past century may be considered a very large uncontrolled experiment that may have contributed to increased societal burdens of aggression, depression, and cardiovascular mortality. Conversely, actively lowering LA intake must be carefully considered because of the large potential effects on agricultural economies. Alternative soybean variants or other sources of seed oils could be used to reduce LA intakes to levels currently seen in countries such as the Philippines, resulting in up to one-tenth lower estimated allowances for n−3 LCFAs as a percentage of energy. The limited worldwide fisheries and aquaculture production would be more likely to be able to meet world needs. Because LA constitutes such a large percent of calories in the US diet, it seems prudent to conduct large-scale intervention trials to determine whether lowering intakes can reduce cardiovascular risk and psychiatric morbidity. Increasing tissue concentrations of n−3 LCFAs on a population level may result in a substantial decrease in health care costs by reducing the illnesses that account for the largest burden of disease worldwide.

Although the term *highly unsaturated fatty acids* (*HUFAs*) is preferred by the authors, *LCFAs* was used for stylistic commonality for this conference. JRH, LRGN, TLB, JAR, and WEML each contributed to the writing of the article, the data analysis, and the interpretation. JRH originated the conceptual framework of the article. LRGN and JAR performed most of the calculations. None of the authors had a personal or financial conflict of interest.

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