Dietary Fat Quality and Coronary Heart Disease Prevention: A Unified Theory Based on Evolutionary, Historical, Global, and Modern Perspectives

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Opinion statement

A large and growing body of evidence indicates that dietary fatty acids regulate crucial metabolic processes involved in the pathogenesis of coronary heart disease (CHD). Despite this evidence, optimal dietary fatty acid intakes for CHD prevention remain unclear. Significant gaps in the modern nutrition literature and contradictions in its interpretation have precluded broad consensus. These shortcomings can be addressed through the incorporation of evolutionary, historical, and global perspectives. The objective of this review is to propose a unified theory of optimal dietary fatty acid intake for CHD prevention that integrates critical insights from evolutionary, historical, global, and modern perspectives. This broad approach may be more likely than previous methods to characterize optimal fatty acid intakes.

Introduction

Coronary heart disease (CHD) incidence and mortality reflect complex interactions between genetic susceptibilities and environmental factors. Although several CHD susceptibility genes have been identified [1], several lines of evidence indicate that environment rather than genetics is the main driver of CHD risk [2]. Globally, age-adjusted CHD incidence and mortality vary as much as 10-fold across populations [3,4]. CHD incidence and risk factors are sensitive to lifestyle changes. When immigrants from traditionally low-risk regions adopt the habits of high-risk populations, their CHD incidence rises to approach that of resident inhabitants, especially with increasing duration of residence [5–7].

For instance, CHD is historically far more common in the United States than in Japan [4]. Among men of Japanese ancestry, CHD risk is lowest in Japan, intermediate in Hawaii, and highest in California [8,9]. These differences appear to reflect the replacement of traditional Japanese cultural traditions with Western habits [8]. Indeed, Japanese Americans who maintained traditional customs and habits had a CHD risk similar to that of their counterparts residing in Japan, whereas those who adopted Western culture had a three- to fivefold excess in CHD prevalence [8].

CARDIOMETABOLIC PROCESSES

As the source of virtually all structural and functional molecules in the human body, diet is perhaps the most important environmental determinant of health. Mounting evidence suggests that global populations with very low CHD rates share certain dietary characteristics, especially dietary fatty acid intakes [10–13]. However, the relationships between dietary fats and CHD are considerably more complex than was originally believed. The conventional narrative of the relationship between dietary fats and CHD, known as the "lipid hypothesis," was founded on the principle that low-density lipoprotein (LDL) cholesterol is the major CHD risk factor and is the primary risk factor that can be readily modified via diet. Substantial evidence has since accumulated that dietary fatty acids play critical regulatory roles in a host of biochemical processes implicated in CHD pathogenesis, including inflammation [14], endothelial activation [14], smooth muscle cell proliferation [15], thrombogenesis [16], adipogenesis [17], oxidative stress [18], glucose and insulin metabolism [19], plaque rupture [20], and arrhythmogenesis [21].

EVOLUTIONARY PERSPECTIVE: ANCESTRAL HUMAN DIETS

By analyzing ancient human and animal remains, studying the diets of modern hunter-gatherers, and comparing nutrient compositions of wild and domesticated plant and animal foods, evolutionary biologists have gained insights into ancestral human diets. Although dietary patterns varied by latitude, season, weather, culture, and other variables, all ancestral diets shared key features. Food sources were limited to unprocessed plants foraged, and unprocessed land and marine animals hunted, from the proximate environment. Hunted animals consumed only natural foods from local environments. Until recently, human diets consisted of combinations of wild animal carcasses (including brains, bone marrow, and organs), shellfish, fish, fruits, leafy vegetables, mushrooms, insects, larvae, nuts, and seasonal honey and eggs. These diets provided balance in critical metabolic processes, favored health, and allowed our ancestors to thrive, reproduce, and pass their genes to subsequent generations [22]. Modern humans are physiologically adapted to the diets of our ancestors, which shaped our genetic makeup [22].

Fatty acid intake in modern Western societies scarcely resembles that of our ancestors [22,23]. The first major change occurred between 5000 and 10,000 years ago with the advent of the Agricultural Revolution and animal husbandry [22], leading to widespread replacement of traditional foods with cereal grains and dairy. More recently, the Industrial Revolution heralded the onset of advances in crop manipulation, intensive animal-rearing practices, and food processing, which radically altered both the qualitative and quantitative balance of dietary fatty acids in the food supply [24]. Through food processing techniques such as hydrogenation of vegetable oils, novel bioactive compounds, including industrially produced *trans*-fatty acids (TFAs), were introduced into the modern food supply [22]. Ingestion of omega-3 (n-3) polyunsaturated fatty acids (PUFAs) has declined sharply, whereas intake of omega-6 (n-6) PUFAs and other fatty acids has risen to unprecedented levels [22].

These drastic changes occurred over less than 200 years, insufficient time for genetic adaptation [22]. As a consequence, individuals consuming Western diets may no longer be consuming fatty acids within genetically determined ranges, disturbing metabolic processes ranging from inflammation and plaque rupture to thrombosis and arrhythmogenesis [22]. These metabolic derangements play major roles in the modern epidemic of CHD.

GLOBAL PERSPECTIVES

Investigators have examined diets of populations around the globe, including groups in which CHD mortality differs as much as 10-fold [3,4]. These efforts have defined common characteristics of modern populations with very low CHD risk. Among these groups, total fat intake ranges from less than 15% of energy in portions of rural China [25] to more than 40% of energy in some Mediterranean populations [26], indicating that total fat quantity matters less than fat quality. All these healthy populations have 1) minimal intake of industrially produced TFAs, 2) high intakes of n-3 PUFAs, and 3) low intakes of n-6 PUFAs. Most also consume low quantities of saturated fatty acids (SFAs) and relatively high amounts of monounsaturated fatty acids (MUFAs), with a few notable exceptions, including Pacific Islander populations of Tokelau (high SFA intake) [27] and Kitava (high SFA intake) [28], the Masai of East Africa (high SFA intake) [29], and many Asian populations (low MUFA and low SFA intake) [10].

Controlled trials in which Western dieters adopted the dietary patterns of populations with low CHD risk provide further support that dietary fatty acids play a crucial role in CHD pathogenesis [30,31]. The Lyon Diet–Heart Study (LDHS) was a randomized trial with 302 post–myocardial infarction (MI) patients assigned to a traditional Mediterranean diet: high MUFA and n-3 α-linolenic acid (ALA) intake and restricted n-6 linoleic acid (LA) and SFA consumption. Controls consumed a "prudent" diet similar to that recommended throughout the Western world today. After a 27-month follow-up, coronary event and mortality rates were 73% and 70% lower, respectively, in the Mediterranean diet group [31]. Similar trends were seen at a mean follow-up of 4 years [30]. Because no differences in total, LDL, or high-density lipoprotein (HDL) cholesterol levels were seen between the two groups [31], metabolic processes other than lipoprotein metabolism accounted for the CHD risk reduction. Interestingly, plasma fatty acid profiles of subjects on the Mediterranean diet were nearly identical to those on Kohama, a Japanese island renowned for

Table 1. Major dietary sources of fatty acids

Fatty acids*	Major sources*	Notes
TFAs	Most TFAs are supplied by 3 categories of food items: Household shortenings and margarines Foods fried in PHVOs Baked goods	Beef and dairy contain small amounts of *trans*-vaccenic acid, which has metabolic effects different from those of synthetic TFAs.
SFAs	The main dietary SFAs are laurate (12:0), myristate (14:0), palmitate (16:0), and stearate (18:0). Grain-fed animal meats and dairy products are rich sources of palmitate and, to a lesser extent, stearate. Other sources include palm oil, which consists primarily of palmitate, and cocoa butter, a major source of stearate. Coconut and palm kernel oils consist primarily of laurate and myristate.	
MUFAs	The primary dietary MUFA is oleate (18:1n-9). Concentrated sources include whole olives, olive oil, canola oil, avocados, and many nuts, especially macadamias, cashews, and almonds.	Dairy and other animal fats provide significant amounts of oleate, although it is accompanied by high quantities of palmitate and other SFAs.
Medium-chain n-6 PUFAs: LA (18:2n-6)	Highly concentrated in most vegetable and seed oils consumed in the US, especially safflower, sunflower, corn, cottonseed, and soybean oils	
Medium-chain n-3 PUFAs: ALA (8:3n-3)	Rich sources include flaxseed, canola oil, and walnuts. Green leafy vegetables provide smaller but significant amounts.	Soybean oil–based salad dressing and mayonnaise, which provide the bulk of US ALA intake [74], are accompanied by large quantities of n-6 LA.
Long-chain n-6 PUFAs: AA (20:4n-6)	Major sources include eggs, poultry, beef, pork, liver, tropical fish, and certain farm-raised fish.	
Long-chain n-3 PUFAs: EPA (20:5n-3), DHA (22:6n-3)	Rich sources include mackerel, herring, trout, salmon, anchovies, sardines, tuna, and oysters. Less concentrated sources include shrimp, mussels, squid, and scallops. Muscle tissue of wild game, such as elk, deer, and antelope, and pasture-fed cattle also contains EPA+DHA, although in smaller amounts [48].	Modern grain-fed animal products (ie, meats, eggs) contain far lower concentrations of n-3 EPA+DHA than more naturally raised counterparts and wild animals [48].

*Numbers in parentheses represent molecular formulas (eg, 12:0 = 0 double bonds).
AA—arachidonic acid; ALA—α-linolenic acid; DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid; MUFA—monounsaturated fatty acid; n-3—omega-3; n-6—omega-6; n-9—omega-9; LA—linoleic acid; PHVO—partially hydrogenated vegetable oil; PUFA—polyunsaturated fatty acid; SFA—saturated fatty acid; TFA—*trans*-fatty acid.

exceptional longevity [32]. LDHS results indicate that dietary changes can profoundly reduce CHD risk, perhaps more effectively than pharmaceutical approaches.

Recent advances in disciplines ranging from molecular biology to anthropology have provided novel insights into the relationship between dietary fat intakes and CHD risk. As a result, the original lipid hypothesis is evolving into a multidimensional conceptual framework that incorporates evolutionary, historical, global, and modern experimental perspectives. In the following section, we will summarize what is known about each of seven critically important fat categories, providing a solid foundation on which to build a unified theory of optimal fat intake for CHD prevention.

Dietary fatty acids

- See Table 1 for a summary of the major dietary sources of fatty acids.

trans-Fatty acids

Possible mechanisms of action

TFA intake is associated with elevated levels of LDL cholesterol, small dense LDL subtype, lipoprotein(a), and triglycerides, as well as reduced HDL

cholesterol levels [33]. TFAs also have been linked to systemic inflammation, endothelial dysfunction, and sudden cardiac death [33]. In a primate feeding study, *trans*-fat intake induced visceral fat accumulation, insulin resistance, and weight gain, even in the absence of caloric excess [34].

Global intake

Synthetic TFA consumption varies widely across populations, with mean intakes ranging from 0% of energy in modern hunter-gatherers, to less than 0.5% in Asian/Pacific countries, to more than 5% in subpopulations of some Western countries [35].

Modern intake

In 1999, TFAs accounted for roughly 2% to 3% of US energy [36]. Current per capita US intake of TFAs is difficult to estimate because of a recent decline in TFA content of foods in response to 2006 US Food and Drug Administration–mandated labeling requirements. Substitution of nonhydrogenated oils by fast food companies has reduced intake further. Pending legislation banning restaurant use of partially hydrogenated vegetable oils (PHVOs) and greater consumer awareness promise to further reduce TFA consumption.

Historical/evolutionary intake

Synthetic TFAs were absent from human diets before the invention of hydrogenation around 1900. Beginning in 1911, with the commercialization of Crisco (partially hydrogenated cottonseed oil), significant quantities of TFAs entered the food supply. The low cost of PHVOs made them attractive alternatives to butter and lard, and their use gradually climbed over the ensuing decades. By 1972, per capita intake had increased to more than 11 g/d, roughly 5% of energy [37]. In the 1970s and 1980s, landmark studies linked SFA intake to CHD [4]. Throughout the 1980s and 1990s TFA-rich margarines were widely recommended as "heart healthy" alternatives to butters rich in SFA and cholesterol.

Growing evidence of adverse cardiometabolic effects of TFAs has major implications for the interpretation of landmark controlled dietary trials. For instance, the Oslo Diet–Heart Study (ODHS) [38], widely cited to support the hypothesis that high n-6 LA diets are cardioprotective, is a major basis for current dietary guidelines urging high LA intake [39••]. However, in the two decades before the study began, Oslo males had a sevenfold increase in incidence of first MI (from 9.0 per 10,000 in 1945 to 65 per 10,000 in 1961) [38]. This rapid rise coincided with the widespread use of partially hydrogenated fish and vegetable oil margarines, which accounted for 65 g/d per person (25% of energy). Importantly, experimental dieters replaced margarines with nonhydrogenated LA-rich oils, whereas the control diet was unchanged. Hence, the historical context of dietary trials must be taken into consideration; failure to do so may lead to flawed recommendations.

Spectrum of evidence

The most compelling evidence linking TFAs to CHD is observational in nature. Cross-cultural [4] and prospective cohort studies [40] have reported significant positive associations between TFA intake and CHD risk. On a per calorie basis, TFAs have a much stronger correlation with CHD than do SFAs [40,41].

Conclusion

Reduction or elimination of TFAs is likely to have significant beneficial cardiometabolic effects and is unlikely to do harm.

Saturated fatty acids

Possible mechanisms of action

Evidence that SFAs elevate total and LDL cholesterol concentrations is the basis for guidelines to reduce SFA intakes. However, the metabolic aspects of individual SFAs are complex and lack uniformity. For example, stearate does not appear to increase LDL [42], and several SFAs enhance HDL metabolism [43]. Laurate and stearate reduce the total cholesterol/HDL ratio, whereas myristate has no effect [43]. Palmitate, on the other hand, raises LDL and the LDL/HDL ratio. Palmitate also may enhance thrombogenesis when substituted for stearate [44]. There is little evidence to support a role for SFAs in other cardiometabolic processes, although this is under investigation.

Global intake

SFA intakes vary widely across populations, with mean intake ranging from less than 5% of energy in rural China [25] to more than 40% of energy in the Pacific island of Tokelau [27]. Virtually all SFAs in Tokelau derive from coconut oil and therefore consist of laurate and myristate.

Historical/modern intake

US SFA intake declined from 16% to 12% of energy between 1977 and 1995 in response to cholesterol-lowering dietary guidelines [45]. US adults consume an average of 11% to 12% of energy from SFAs [46], mostly from grain-fed meats and dairy products. Palmitate accounts for more than half of US SFA intake.

Evolutionary intake

SFAs accounted for an estimated 10% to 15% of energy of preagricultural humans, mostly from wild game [47], which contains less total SFAs, less palmitate, and a higher proportion of stearate than commercial meats widely available today [48]. Grain-fed cattle, which account for more than 95% of US beef consumption, contain two to four times more SFAs than animals raised naturally [48]. Dairy was not available before the onset of animal husbandry 6000 to 10,000 years ago [22].

Spectrum of evidence

The Seven Country Study, a cross-cultural analysis, reported strong positive associations among a population's average SFA intake, serum total cholesterol concentrations, and 25-year death rates from CHD [49]. However, it is important to note that several groups with very high SFA intakes from coconut fat (up to 40% of energy) and apparently low CHD rates have since been identified [27,28]. In the Nurses' Health Study, a large prospective cohort study, a weak but significant positive association between SFA intake and CHD risk was initially seen [41]. With long-term follow-up, this association was no longer significant [40]. Any association between SFAs and CHD appears to be a small fraction of that observed for TFAs [41]. Other observational studies and dietary trials have been unconvincing or even contradictory [50]. In general, experimental evidence does not support a robust link between SFA intake and CHD risk [51].

Conclusion

Replacement of SFAs, especially palmitate, with MUFAs may provide moderate cardiometabolic benefits, and is unlikely to do harm. However, SFA reduction does not appear to be the most important dietary modification for CHD risk reduction.

Monounsaturated fatty acids

Possible mechanisms of action

MUFA consumption is associated with improved lipoprotein parameters [43], reduced LDL oxidation [18], improved insulin sensitivity [19], and reduced thrombogenesis [52].

Global intake

MUFA intakes vary widely across populations, with mean intakes ranging from about 7% of energy in parts of Asia [25] to more than 20% of energy in some Mediterranean regions [26], where most MUFAs derive from olives and olive oil.

Modern intake

MUFA intake accounts for approximately 13% of US energy [46].

Evolutionary intake

MUFAs accounted for about half of total fat and roughly 16% to 25% of total energy [48,53] for preagricultural humans, with wild animal meats, bone marrow, and nuts providing concentrated sources. The diets of wild ruminants (eg, deer, antelope) consist of grasses, seeds, low-hanging branches, moss, clovers, and flowers [54]. Modern animal-rearing practices have profoundly altered the composition of beef, poultry, and other meats, resulting in replacement of MUFAs with SFAs, especially palmitate [22]. Modern pasture-fed meats have a fatty acid composition similar to that of wild meats [48].

Spectrum of evidence

Mediterranean populations consuming diets rich in MUFAs have among the lowest CHD rates in the world [3,4]. However, populations with relatively low MUFA intakes and low CHD risk do exist, most notably in Japan [10]. Some, but not all, observational studies have reported an inverse association between MUFAs and CHD risk [40,41]. No large controlled trials have evaluated replacement of MUFAs as an independent variable in relation to CHD outcomes. However, in the context of the Mediterranean dietary pattern (restricted n-6 linoleate and SFAs, increased fiber and antioxidants), high-MUFA diets are associated with significant reduction in CHD events compared with Western dietary patterns [30,31].

Conclusion

Substitution of MUFAs for TFAs, palmitate, and perhaps other SFAs may have beneficial cardiometabolic effects and is unlikely to do harm.

Polyunsaturated fatty acids

- Dietary PUFAs can be broadly grouped into four main categories: 1) medium-chain n-6 (linoleic [LA]), 2) medium-chain n-3 (α-linolenic [ALA]), 3) long-chain n-6 (arachidonic [AA]), and 4) long-chain n-3 (eicosapentaenoic [EPA] and docosahexaenoic [DHA]) acids. Medium-chain PUFAs are provided mainly by plant sources; long-chain PUFAs are supplied only by animal sources. Dietary n-6 and n-3 PUFAs interact with one another in a complex network [55]. Tissue accumulation and activity of medium- and long-chain n-6 and n-3 PUFAs depend on both relative and absolute intake of all five of these molecules [55–57]. Hence, it is imperative to consider intakes of these PUFAs in the context of one another.

Medium-chain omega-6 PUFAs: linoleic acid

Possible mechanisms of action

Evidence that LA reduces LDL cholesterol when substituted for SFAs or TFAs is the basis for modern recommendations urging high LA intake. However, high LA intake also reduces tissue n-3 EPA and DHA (EPA+DHA) levels, possibly increasing CHD risk [55,58]. In addition, long-term reduction of n-6 LA to levels consistent with evolutionary intakes appears to reduce tissue n-6 AA levels [31,59], although this requires confirmation in humans.

Modern intake

LA accounts for 6% to 7% of energy and nearly 90% of PUFA intake in the United States [46].

Global intake

LA consumption varies widely across populations, with mean intakes ranging from less than 1% of energy in the Philippines [60] to more than 8% of energy in Israel [61].

Evolutionary/historical intake

Preagricultural humans living on the African grassland consumed roughly 3% of energy from LA, mostly from wild animal meats [62]. As far back as 160,000 years ago, some ancient humans living in coastal caves and harvesting marine resources [63••] would have consumed far less LA (perhaps 1% of energy). US LA intake increased threefold from 1909 to 2009, driven primarily by solvent extraction of vegetable and seed oils [64]. With no historical or evolutionary precedent, this high LA intake has been termed a "massive uncontrolled human experiment" [65].

Spectrum of evidence

Traditional Mediterranean, rural Japanese, and other populations with very low CHD risk have uniformly low LA intakes [26,32]. Two US prospective cohort studies have reported inverse associations between LA intake and CHD risk [41,66]. However, because LA intake was uniformly high, severalfold higher than evolutionary intakes and those of modern groups with very low CHD rates [32], these studies provide little insight into optimal LA intakes. Moreover, both studies relied on food frequency questionnaires, which have well-known limitations [67] and may not be able to disentangle the effects of LA and n-3 ALA. Controlled trials in which high-LA oils replaced TFA- and SFA-rich fats have shown conflicting results [38,68–72], despite the fact that LA was accompanied by large amounts of medium- [38,70] and long-chain n-3 PUFAs [38]. A single small trial testing the specific effects of LA without n-3 PUFAs found increased CHD risk [71]. The only long-term trial that reduced n-6 LA intake to resemble a traditional Mediterranean diet (but still higher than preindustrial LA intake) reduced CHD events and mortality by 70% [31]. Although this does not prove that LA intake has adverse consequences, it clearly indicates that high LA intake is not necessary for profound CHD risk reduction.

Conclusion

The replacement of LA-rich oils with MUFA-rich oils (eg, olive oil) may provide considerable cardiometabolic benefits and is unlikely to do harm.

Medium-chain omega-3 PUFAs: α-linolenic acid

Possible mechanisms of action

ALA appears to have direct cardioprotective properties [73] as well as indirect benefits through hepatic conversion to EPA (see the section on EPA+DHA). High intakes of n-6 LA, characteristic of the typical Western diet, interfere with both hepatic conversion of ALA to EPA and tissue accumulation of EPA+DHA [55,58,59]. Hence, maximal cardiometabolic benefits of ALA occur in the context of low-LA diets.

Modern intake

ALA accounts for roughly 0.6% of US energy [46].

Global intake

ALA consumption varies across populations, with modern intakes uniformly lower than evolutionary estimates [62].

Historical/modern intake

Preagricultural humans living on the African grassland consumed an estimated 2% to 5% of energy from ALA, an amount similar to that of n-6 LA [62]. Modern grain-fed animal products contain only a small fraction of the n-3 ALA present in wild animals. Most US ALA is derived from soybean oil and is therefore accompanied by large quantities of n-6 LA [40].

Spectrum of evidence

Several, but not all, large epidemiologic studies have observed an inverse association between ALA intake and CHD risk [66,74]. Cardioprotective properties of ALA do not appear to be as robust as those of n-3 EPA+DHA [75]. The LDHS demonstrated impressive reduction of CHD events and mortality with high ALA intakes in the context of a low-LA Mediterranean diet [31]. In multivariate analysis, plasma ALA was significantly and inversely correlated with risk of recurrence [30].

Conclusion

Consumption of moderate quantities of n-3 ALA may have considerable cardiometabolic benefits and is unlikely to do harm. ALA is most effective in the context of low-LA diets.

Long-chain omega-6 PUFAs: arachidonic acid

Possible mechanisms of action

AA is a major component of the lipid membranes of every human cell, including platelets, immune cells, and endothelial cells. In response to inflammatory stimuli, AA is enzymatically cleaved and converted to an array of lipid mediators with potent metabolic effects. Although the roles of AA-derived mediators are complex and lack uniformity, they are generally prothrombotic and proinflammatory compared with their n-3 EPA–derived counterparts [16,76]. Indeed, inhibition of AA metabolism accounts for the beneficial effects of aspirin.

Modern intake

AA accounts for approximately 0.1% of US energy. Although intake is modest compared with that of other PUFAs, virtually all dietary AA is available for metabolic conversion into potent lipid mediators [57].

Global intake

Worldwide AA intakes have not been systematically characterized. AA consumption is highest in populations with high intakes of meats and eggs.

Historical/evolutionary intake

Historical AA consumption is a matter of controversy; quantitative estimates depend on whether early humans lived at the land–water interface or the African grassland [62,77]. Early humans would have consumed considerably less AA in a marine environment [63••]. Modern agribusiness practices have radically altered the n-6 AA and n-3 EPA+DHA contents of domesticated animal meats. Grain-fed livestock contain moderate amounts of AA but only a tiny fraction of the EPA+DHA of their wild and pasture-fed counterparts [48]. Similar changes have occurred in eggs, poultry, and farm-raised fish [78].

Spectrum of evidence

Mean population tissue proportions of AA and other long-chain n-6 PUFAs have a marked positive correlation with CHD mortality [79]. Although adipose tissue AA has been positively linked to increased CHD events [80], the relationship between plasma AA concentrations and CHD events within populations is less clear [81]. No controlled trial has examined the effects of dietary AA on CHD risk.

Conclusion

Partial replacement of n-6 AA with n-3 EPA+DHA may provide significant cardiometabolic benefit and is unlikely to do harm.

Long-chain omega-3 PUFAs: eicosapentaenoic acid and docosahexaenoic acid

Possible mechanisms of action

EPA+DHA have a wide array of beneficial cardiometabolic effects, including reduction of ventricular arrhythmias [21]; competition with n-6 AA, which reduces platelet aggregation [16]; enhanced lipoprotein profile [75]; inhibition of early and late inflammatory atherogenesis [14]; improved endothelial function [14]; and plaque stabilization [20].

Global intake

EPA+DHA intakes vary widely across populations, with mean intakes ranging from 0.02% of energy in Bulgaria to more than 0.40% of energy in Iceland and Japan [60].

Modern intake

EPA+DHA account for 110 mg/d, roughly 0.05% of US energy intake [46]. As much as 25% of the US population consumes no detectable EPA or DHA [82].

Historical/evolutionary intake

Like AA intakes, EPA+DHA consumption estimates depend on whether early humans lived on the grassland or at the land–water interface. Humans subsisting on grassland diets consumed at least 660 mg/d of EPA+DHA [62], about six times the amount consumed by modern Americans, whereas estimates of early humans at the land–water interface are considerably higher [77]. Modern grain-fed animal products contain far lower concentrations of EPA+DHA than grass-fed counterparts and wild animals [48]. Historically speaking, the lack of EPA+DHA in meats is unprecedented.

Spectrum of evidence

Populations with high intakes of EPA+DHA–rich foods generally have low CHD risk [32,79]. Likewise, mean population tissue proportions of long-chain n-3 PUFAs have a strong inverse correlation with CHD mortality [79]. Observational studies suggest that EPA+DHA reduce CHD mortality. In a Japanese cohort followed up over 10 years, EPA+DHA intake was associated with a significant reduction in the risk of nonfatal coronary events and total MIs [83••]. In fact, CHD risk continued to decline at intakes up to 20 times the mean US intake [83••]. Erythrocyte membrane EPA+DHA proportions (n-3 index) are inversely associated with CHD mortality [84]. Controlled trials indicate that EPA+DHA are effective in secondary prevention. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) Prevenzione study, an EPA+DHA intake of 850 mg/d reduced total mortality by 20% and sudden death by 45% in post-MI patients [85].

Conclusion

Increased consumption of n-3 EPA+DHA provides significant cardiometabolic benefit and is unlikely to do harm. A long-term increase in EPA+DHA intake is perhaps the most beneficial isolated dietary modification for reducing CHD events and mortality.

Future directions

- The totality of worldwide medical and scientific evidence indicates that wide ranges of total fat intakes are compatible with a healthy diet and that fat quality, rather than total fat quantity, plays a central role in determining CHD risk. Integrating evolutionary, historical, and global perspectives with modern experimental evidence provides a broader framework for identifying key elements of optimal diets for CHD prevention. This approach also may be less likely to cause harm. As demonstrated, convergence of numerous lines of evidence leads to the following conclusions:
  - n-3 PUFAs, especially long-chain n-3 PUFAs, reduce CHD risk. Increasing intake is unlikely to cause harm.
  - Industrially produced TFAs increase CHD risk. Restricting or eliminating TFA intake is unlikely to cause harm.
  - MUFAs possibly reduce CHD risk. Substituting MUFAs for TFAs or SFAs, especially palmitate, is unlikely to cause harm.
  - High consumption of palmitate may increase CHD risk. The relationship of stearate, laurate, and myristate to CHD is less clear. Partial substitution of MUFAs for palmitate, and perhaps other SFAs, may reduce CHD risk and is unlikely to cause harm.
  - Optimal n-6 LA intake for CHD prevention is a matter of controversy. US health promotion agencies recommend high LA consumption [39••] despite the fact that 1) modern Western LA intake is unnaturally high by evolutionary, historical, and global standards, and 2) populations with very low CHD risk have uniformly low LA intakes. CHD risk declined markedly in the sole long-term randomized trial in which LA was lowered as part of a Mediterranean diet, indicating that high LA intake is not a requirement for CHD risk reduction. Controlled trials and observational studies comparing high with very high LA intakes are insufficient for drawing conclusions regarding optimal

LA intake. In light of current guidelines urging high LA intake, the CHD impact of lowering LA to preindustrial levels is an issue of major public health importance. For now, the replacement of LA-rich oils with MUFA-rich oils (eg, olive oil) may provide considerable cardiometabolic benefits and is unlikely to do harm.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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