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Fish Intake, Contaminants, and Human Health: Evaluating the Risks and the Benefits Part 2 – Health Risks and Optimal Intakes

By DARIUSH MOZAFFARIAN, MD, DRPH

This two-part report summarizes findings from a recent publication in the *Journal of the American Medical Association*.[1] Part 1, in the October issue of *Cardiology Rounds*, discussed the potential health benefits of fish and fish oil intake. Part 2, in this issue, discusses the potential health risks and describes optimal intakes for different populations. The tables and figures in this report are adapted from *JAMA*, October 18, 2006; 296:1886-99, © 2006, American Medical Association, all rights reserved.

Health effects of fish intake – controversy and confusion

Since low rates of coronary heart disease (CHD) death were observed in Greenland Eskimos consuming high quantities of seafood,[2] evidence from animal-experimental, observational, and clinical research has further supported a protective effect of fish consumption on risk of CHD death. Two marine n-3 polyunsaturated fatty acids (n-3 PUFAs) – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – have been identified as the likely active constituents.[3-21] On the other hand, there is growing concern over the potentially harmful effects of mercury, dioxins, and polychlorinated biphenyls (PCBs) that are present in some fish species.[22-29] As a result, there are contradictory messages on the risks and benefits of fish intake, causing controversy and confusion over the health effects of fish consumption.[30,31]

Health risks of mercury

Mercury is emitted into the atmosphere from several sources, including volcanoes, coal-fired electric power plants, gold mining, institutional boilers, chlorine production, and waste incineration. From the atmosphere, mercury cycles from rainwater into lakes and oceans, where it is converted by the action of microorganisms into organic methylmercury. Compared with inorganic or elemental mercury, methylmercury bioaccumulates in aquatic food chains and has greater potential toxicity than inorganic mercury.[22,23,25] For example, inorganic mercury is poorly absorbed in the gastrointestinal tract following consumption, and elemental mercury does not readily cross tissue barriers, while methylmercury is well absorbed and actively transported into tissues by a widely distributed carrier protein.[22]

The concentration of methylmercury in any given fish species depends on the degree of local environmental contamination and on the predatory nature and lifespan of the species. Longer-living, larger predators, such as swordfish or shark, have higher tissue concentrations, while shorter-lived or smaller species, such as salmon or shellfish, have very low concentrations (Table 1). Methylmercury content of fish is not significantly altered by preparation methods.[22]

Following uptake into tissues, mercury can bind to the sulfhydryl groups of enzymes, ion channels, and receptors, which can inhibit important antioxidant systems and increase the production of reactive oxygen species and free radicals.[22, 24] Health effects of very high doses of mercury exposure following occupational or industrial accidents are well-documented and include paresthesias, ataxia, and sensory abnormalities in adults, and delayed cognitive and neuromuscular development in children following *in utero* exposure.[22,32] However, the health effects of chronic low level mercury exposure – i.e., that seen with typical fish consumption – are less well-established. This evidence is reviewed herein.

Early neurodevelopment

Methylmercury crosses the placenta, and exposure to the fetus is a function of maternal exposure.[33] Following very high gestational exposure, severe neurodevelopmental abnormalities can occur in children. This was seen, for example, following industrial accidents in Japan in the 1950s and Iraq in 1971, when

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Table 1: Levels of n-3 fatty acids and contaminants in commonly consumed fish, shellfish, and other foods

	EPA + DHA, mg per serving (serving size)	Selenium, µg/g (parts per million)	Mercury, µg/g (parts per million)	PCBs, ng/g (parts per billion)	Dioxins, TEQ pg/g (parts per trillion)
FDA action level	n/a	n/a	1.0	2000	none
Fish					
Anchovy	1165 (2 oz)	0.68	<0.05		0.35 (1997-98)
Catfish, Farmed	253 (5 oz)	0.15	<0.05	<50 (1997)	0.52 (1995-97)
Cod, Atlantic	284 (6.3 oz)	0.38	0.10		0.10 (1995-97)
Fish Burger, Fast Food	337 (2.2 oz)	0.17	<0.05	8 (2001)	0.06 (2001)
Fish Sticks, Frozen	193 (3.2 oz)	0.17	<0.05		0.04 (2001)
Golden Bass (Tilefish)	1,358 (5.3 oz)	0.52	1.45		
Halibut	740 (5.6 oz)	0.47	0.25		1.00 (1995-97)
Herring, Atlantic	1,712 (3 oz)	0.47	<0.05		0.97 (1995-98)
Mackerel, Atlantic	1,059 (3.1 oz)	0.52	0.05		0.60 (1997-98)
Mackerel, King	618 (5.4 oz)	0.47	0.73		
Salmon, Farmed†	4,504 (6 oz)	0.41	<0.05	25* (2001-03)	0.61 (2001-03)
Salmon, Wild†	1,774 (6 oz)	0.46	<0.05	1.8* (2002)	0.19 (2002)
Sardines	556 (2 oz)	0.53	<0.05	40 (2001-03)	0.31 (2001-03)
Shark	585 (3 oz)	0.34	0.99		
Swordfish	868 (3.7 oz)	0.62	0.98		
Trout	581 (2.2 oz)	0.15	0.07	11 (2002)	0.44‡ (2002)
Tuna, Light (Skipjack)†	228 (3 oz)	0.80	0.12	45 (2001)	0.02 (1995-98)
Tuna, White (Albacore)†	733 (3 oz)	0.66	0.35	100 (2001-03)	0.23 (2001-03)
Shellfish					
Crab	351 (3 oz)	0.40	0.09	6 (2002)	0.55‡ (2002)
Scallops	310 (3 oz)	0.28	<0.05		0.16 (1998)
Shrimp	267 (3 oz)	0.40	<0.05	1.1 (2002)	0.09‡ (2002)
Other foods					
Beef	0	0.19	0	22 (2001)	0.20 (1995-2001)
Butter	0	<0.05	0	70 (2001)	0.44 (1995-2001)
Cheese	0	0.22	0		0.45 (1995-2001)
Chicken	0	0.23	0	32 (2001)	0.11 (1995-2001)
Eggs	22 (1 egg)	0.23	0	19 (2001)	0.29 (1998-2001)
Milk	0	0.02	0		0.07 (1995-2001)

Average values shown (Mozaffarian and Rimm[1]), which may vary due to methodologic, geographic, temporal, and fish-to-fish differences. Values for PCBs and dioxins may overestimate current levels because contaminant levels in most foods, including fish species, are decreasing over time (eg, TEQs decreased by 33%-81% in meats and 66%-77% in salmon and tuna fish between 1995 and 2003); year of sampling is given in parenthesis.

* Values including the fish skin; levels may be lower in the edible portion.

† For the same specific species, there are minimal differences in nutritional or contaminant content of canned vs. fresh salmon or tuna. However, different species are typically canned vs. sold fresh. For salmon, differences between species are small compared with differences between farmed and wild salmon. For tuna, canned light (skipjack) tuna and fresh yellowfin/ahi tuna are more similar overall, while canned white (albacore) tuna and fresh bluefin tuna are more similar overall.

‡ Includes dioxin-like PCBs. TEQ = Toxic equivalence.

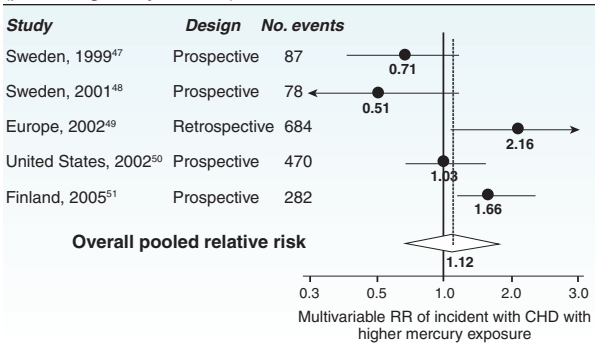
mothers consumed highly contaminated fish (mercury content = 10-30 ppm) or highly contaminated grain (maternal intake = 710-5700 µg/kg/d; maternal hair mercury = 18-598 ppm), respectively.[22,32] More typical methylmercury exposures from fish consumption are far lower. For example, among U.S. women of childbearing age, the median (10th, 95th percentiles) levels of hair mercury were 0.19 ppm (0.04, 1.73) overall, and 0.34 ppm (0.09, 2.75) among women who consumed 3+ servings of fish per month.[34] These low exposure levels do not produce clinically detectable neurologic symptoms or signs in children. Several prospective studies have evaluated whether subclinical effects, detectable with specialized testing, might occur.[35-43] In studies in the Faroe Islands,[35,36] New Zealand,[37,38] and Poland,[39] higher gestational mercury exposure was associated with lower scores on some neurologic tests (eg, finger tapping or naming tests), but not on most other neurologic tests. In contrast, in the Seychelles, higher gestational mercury exposure was associated with *higher* scores on some neurologic tests.[40,41]

In a study of U.S. infants, maternal fish intake during gestation was associated with better visual recognition memory scores, while maternal hair mercury was associated with lower visual recognition memory scores,[42] suggesting that overall fish consumption (which provides DHA, likely beneficial for neurodevelopment; see Part 1) and methylmercury exposure may have opposing effects. Among British children, gestational mercury exposure was not associated with neurodevelopmental scores; in contrast, both maternal and infant fish intake were associated with better neurodevelopmental scores.[43] Several other studies have not seen consistent associations between gestational mercury exposure and neurologic test scores during childhood.[44]

Direct comparisons of these different studies are challenging, due to variation in study designs (prospective vs. cross-sectional), methods for measuring mercury exposure, neurologic tests employed, timing of assessment (infancy vs. childhood), and statistical methods. Some analyses are also limited by incomplete adjustment for potential confounding risk factors, such as socioeconomic status, and multiple statistical testing (eg, 30+ neurologic parameters), increasing the possibility of chance associations. Randomized trials to test the effects of reducing low-level methylmercury exposure during gestation have not been performed. Nevertheless, because some associations with lower neurologic test scores are seen in some studies, and because clinical neurotoxicity is seen following much higher level accidental exposures, it is prudent to conclude that lower exposure levels may produce subclinical neurodevelopmental deficits.

Based on this, the Environmental Protection Agency published a focused Advisory for women of childbearing age, nursing mothers, and young children.[45] The lower 95% confidence limit at which gestational mercury exposure may produce abnormal subclinical neurologic test scores was determined to be 1 µg/kg/day, or ~500 µg/week for a 70 kg woman.[33] For additional safety, this was multiplied by a 10-fold uncertainty factor,

Figure 1: Studies of mercury exposure and risk of coronary heart disease (CHD). Relative risk (•) and 95% CIs (–) are shown comparing the highest to the lowest quantile of mercury exposure after adjustment for other risk factors. Combining results of studies, the relationship was not significant (RR = 1.12, 95% CI, 0.71-1.75, p = 0.62), with significant heterogeneity between studies (p heterogeneity = 0.008).



resulting in a reference dose, the allowable upper limit of daily intake, for methylmercury of 0.1 µg/kg/day (~50 µg/week for a 70 kg woman).[33] Four fish species (shark, swordfish, king mackerel, tilefish) exceed this limit in a single serving (Table 1), so the Advisory recommended that women of childbearing age, nursing mothers, and young children avoid these specific species.[45] Notably, the Advisory also emphasized that women and children should consume a variety of other fish up to 2 servings/week (including up to 1 serving/week of albacore tuna) to receive the important health benefits.[45] It is also relevant that this Advisory was intended only for this specific population, because the importance of this conservative reference dose for health effects in adults is unclear.[46]

Cardiovascular disease

The results of studies of mercury exposure and cardiovascular disease incidence in adults are conflicting (Figure 1),[47-51] providing inconclusive evidence for cardiovascular toxicity of mercury exposure. Of note, in the only 2 studies that observed positive associations between mercury exposure and cardiovascular risk, the *net* effect of fish consumption was still beneficial: compared to those not eating fish or n-3 PUFAs, individuals consuming fish or n-3 PUFAs still had lower risk of heart disease, but the size of this lower risk was somewhat less if their mercury exposure was higher.[49,51,52] This indicates that the major public health question may not be whether consumption of mercury-containing fish increases cardiovascular risk, but whether consumption of such fish would decrease risk even *further* if mercury were not present. This is an important policy question: the potentially attenuated benefits of fish intake due to mercury content must be balanced against the costs and practicality of reducing mercury levels in the environment. However, this question should not obscure the strong evidence for the net cardiovascular benefits of fish consumption (see Part 1). This balance of benefit vs. risk would be most favorable for oily fish species which contain higher amounts of n-3 PUFAs (ie, most mercury-containing ocean fish), compared with lean fish from freshwater sources, which are generally lower in n-3 PUFAs.

Neurologic outcomes

Sensorimotor symptoms in adults, most commonly paresthesias, can be seen following very high methylmercury exposure from accidents[22,32,53] or prolonged high intakes of mercury-containing fish (e.g., 1-2 fish servings per day, including species high in mercury, for >10 years[54]). Such symptoms are typically reversible when mercury exposure is reduced.

Lower levels of mercury exposure (that seen with typical fish intake) do not produce clinically detectable neurologic symptoms or signs in adults. Cross-sectional studies have evaluated whether chronic low level mercury exposure (assessed by hair or blood mercury levels) is associated with subclinical neurologic measures in adults. In studies among Amazon basin and Quebec Cree individuals, both positive and inverse associations were seen between mercury levels and some neurologic measures.[55-57] These results were limited by multiple statistical testing (typically 20-30+ neurologic tests or participant subgroups were evaluated) and by possible inadequate adjustment for other potential risk factors. In a study among U.S. adults, mercury levels were associated with lower visual memory scores (p = 0.01) but better motor and manual dexterity scores (p = 0.02) among 20 different outcomes evaluated.[58] Among elderly Swedish adults, no associations were found between mercury levels and cognitive function.[59] Thus, these studies do not provide clear evidence that low-level methylmercury exposure affects subclinical neurologic outcomes in adults and, if so, what quantities or durations of exposure might be necessary. On the other hand, growing evidence suggests that fish consumption may favorably affect *clinical* neurologic outcomes in adults, including ischemic stroke,[60] cognitive decline and dementia,[61] and depression and other neuropsychiatric disorders.[62, 63]

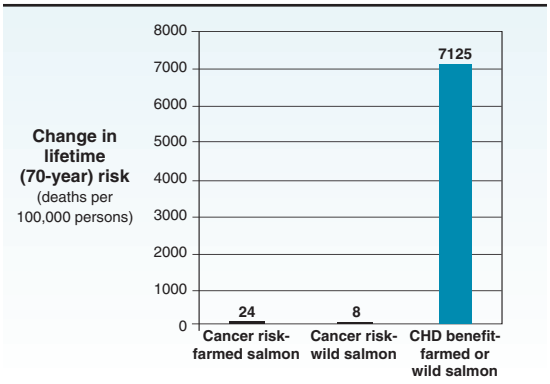
Health risks of dioxins and PCBs

Dioxins (commonly referring to dibenzodioxins and dibenzofurans) are organochlorine by-products of industrial processes involving chlorine, such as waste incineration, paper bleaching, pesticide production, and production of polyvinyl chloride plastics.[28] Regulatory and industry efforts have reduced dioxin emissions >90% since 1987.[28] PCBs are synthetic organochlorine compounds previously used in industrial and commercial processes.[29] Manufacture and processing of PCBs was prohibited in 1977.[29] Thus, environmental levels of these contaminants are steadily declining.[28,64-67] Nevertheless, these contaminants persist for long periods in the environment, and PCBs and dioxins continue to be present in low concentrations in many foods (Table 1).

Cancer risks: Based upon animal experiments and some limited evidence in humans, PCBs and dioxins are carcinogenic.[27,68] There are multiple different chemical structures (congeners) of dioxins and PCBs, each with different potential carcinogenicity. To calculate the potential toxicity of any food, the level of each congener in the food is multiplied by that congener's toxic equivalency factor (standardized against 2,3,7,8-tetrachlorodibenzo-p-dioxin), and these values are summed to determine the Toxic Equivalence (TEQ), the measure of overall potential toxicity. In the U.S., dioxins comprise 72% and PCBs 28% of total TEQ exposure.[69] The major dietary sources of PCBs/dioxins are not fish and shellfish (only 9% of total TEQ), but beef, chicken, and pork (34% of total TEQ); dairy products (30% of total TEQ); and vegetables (22% of total TEQ).[69]

Although the major dietary sources of PCB/dioxin exposure are meats, dairy products, and vegetables, much attention has been given to levels in fish (Table 1). When PCBs and dioxins were measured in farmed and wild salmon,[70,71] levels were similar to several other foods (Table 1). Substantial amounts of n-3 PUFAs were also present in farmed and wild salmon: 4,504 and 1,774 mg EPA+DHA per 6-oz, respectively.[71] A quantitative

Figure 2: Estimated cancer risks and CHD benefits of consumption of farmed and wild salmon, assuming regular intake to provide 1 g EPA+DHA per day over a 70-year lifetime. Based on animal-experimental data and limited studies in humans at much higher doses (and including a 10-fold safety factor), farmed and wild salmon consumption would result in 24 and 8 excess cancer deaths, respectively, per 100,000 individuals. Conversely, based on prospective observational studies and randomized clinical trials in humans, consumption of either farmed or wild salmon would result in 7,125 fewer CHD deaths.



risk-benefit analysis evaluated the potential cancer risks vs. CHD benefits, assuming regular consumption of farmed or wild salmon to provide 1000 mg/d of EPA+DHA over a 70-year lifetime (Figure 2).[72,73] Such consumption would result in 24 and 8 excess cancer deaths per 100,000 lifetimes for farmed and wild salmon, respectively, but also 7,125 fewer CHD deaths per 100,000 lifetimes for either farmed or wild salmon.[72] Thus, for both farmed and wild salmon, the potential benefits far exceeded the potential risks. When age-specific estimates were evaluated,[1] CHD benefits outweighed cancer risks at any age (from 25-34 to 85+ years) by 100-fold to 370-fold for farmed salmon and by 300-fold to >1000-fold for wild salmon.

It is important to note that the estimated CHD benefits are based upon prospective studies and randomized trials in humans (see Part 1), while the estimated cancer risks are based on animal-experimental data and limited studies in humans at high doses. The estimated cancer risks also include a ten-fold safety factor[73] – i.e., the potential risk may be as low as 2.4 and 0.8 cancer deaths per 100,000 lifetimes for farmed and wild salmon, respectively. The estimated cancer risks also assumed a lifetime consumption of salmon to provide 1000 mg/day of EPA+DHA, roughly corresponding to four 6-oz wild salmon every week for 70 years. However, reductions in CHD mortality are likely achieved with much lower intake: ~250 mg/d (see Part 1), or one 6-oz wild salmon serving/week. At this lower intake, CHD benefits would be largely unchanged (~7,125 fewer CHD deaths) while lifetime cancer risk would decrease ~75% (6 and 2 estimated deaths per 100,000 lifetimes for farmed and wild salmon, respectively, or 0.6 and 0.2 estimated deaths per 100,000 lifetimes not including the ten-fold safety factor). Consistent with these very low cancer risks, prospective studies in humans have seen little evidence for effects of fish intake on cancer risk.[74]

Other risks: PCBs and dioxins may have non-cancer risks in adults, such as neurologic or immune system effects.[27-29] On the other hand, consumption of fish may also result in other benefits, such as lowering risk of other cardiovascular outcomes (see Part 1), dementia,[61] neuropsychiatric disorders,[62,63] and inflammatory disorders.[75,76] To alter the estimates of risks vs. benefits meaningfully, such additional possible risks would have to exceed the additional possible benefits by more than 100-fold.

Exposure to PCBs and dioxins during gestation (but not infancy) has been associated with childhood neurodevelopmental deficits in several,[77-83] though not all,[84,85] studies. Because most exposure (>90%) is from meat, dairy, and vegetable sources,[69,86] this concern is not specific to fish consumption, particularly since fish also contains DHA which has likely neurodevelopmental benefits. Nevertheless, because some freshwater fish may have higher levels of PCBs/dioxins, women of childbearing age who consume locally caught freshwater fish from highly contaminated inland sources or who frequently consume (1+ servings/day) commercially sold freshwater fish[86] should consult regional advisories.

Fish oil supplements: Levels of PCBs (0-450 ng/g,[87,88]) and dioxins (0.2-11 TEQ pg/g[89,90]) in fish oil are a function of the levels in the fish species from which the fish oil is derived. Given the small amounts of fish oil consumed (1-3 g/d), the total PCB/dioxin exposure from fish oil intake is extremely low. Fish oil capsules contain very little to no mercury.[91]

Summary of the evidence: optimal intakes

The optimal target intake of n-3 PUFAs may depend on both the population and the outcome of interest. As detailed in Part 1, based on the sum of evidence from prospective studies, clinical trials, and experiments, fish or fish oil intake reduces the risk of CHD death/sudden death. In the general population, 250 mg/d EPA+DHA is a reasonable target intake to reduce CHD mortality. Dietary n-3 PUFAs persist for weeks in tissue membranes,[92] and so this amount can be converted to weekly intake of ~1500-2000 mg. This level of intake can be achieved by consuming one 3-oz serving/wk of farmed salmon, one 6-oz serving/wk of wild salmon or similar oily fish, or more frequent intake of less n-3 PUFA-rich fish (Table 1).

For individuals with established CHD, the American Heart Association and the European Society of Cardiology recommend intake of 1000 mg/d EPA+DHA to reduce CHD mortality.[93,94] While lower doses may be sufficient (see Part 1), this population is at high risk for CHD death and most data to-date are from primary prevention studies. Thus, a target intake of 500-1000 mg/d (consistent with the largest secondary prevention trial to-date[10]) appears reasonable for individuals with established CHD. This level of intake can be achieved by consuming one 6-oz serving/week of fish richest in n-3 PUFAs (such as farmed salmon, anchovies, or herring), more frequently consuming other types of fish (Table 1), or by taking fish oil supplements. The maximum recommended dose of supplements without physician supervision is 3 g/d EPA+DHA.[95] Optimal levels of fish or fish oil intake for other clinical outcomes are not well-established.

For the general population (adolescents, men, and women not of childbearing age), there are no clear health effects of low level methylmercury exposure, and the strength of the evidence and the magnitude of the health benefits greatly exceeds the potential risk. Further investigation is needed to determine whether methylmercury exposure may modestly reduce the cardiovascular benefits of fish intake. For individuals concerned about mercury

exposure, consuming fish 1-2 servings/week and choosing a variety of different seafood will ensure low exposure, since most fish contain very low levels of mercury (Table 1). Individuals with very high fish consumption (≥ 5 servings/week) may choose to limit intake of the few species highest in mercury (Table 1).

DHA appears beneficial for early neurodevelopment. To minimize methylmercury exposure and possible subclinical neurologic harm, women of childbearing age and young children should avoid selected species: shark, swordfish, king mackerel, tilefish, and locally caught sportsfish per local advisories.[26,45] However, emphasis must also be placed on adequate consumption of other fish and shellfish – up to 2 servings/wk, including up to 1 serving/wk of albacore tuna – to provide reasonable DHA[26,45] and avoid further decreases in the already low consumption of seafood by women (74% of women of childbearing age and 85% of pregnant women consume <6 oz/week).[96, 97]

Continued efforts to limit environmental contamination from organochlorine compounds are appropriate. However, the levels of PCBs and dioxins in fish are low, similar to levels in several other foods, and the associated possible risks are far smaller than the health benefits of fish intake. Thus, concern over PCBs/dioxins should not impact individual decisions regarding fish consumption (for locally caught freshwater fish, women of childbearing age should consult regional advisories).

In conclusion, the potential risks of fish intake must be considered in the context of the potential benefits. For major health outcomes among adults, the strength of the evidence and potential magnitudes of the benefits of modest fish intake (1-2 servings/week) greatly exceed those of the potential risks. For women of childbearing age, the benefits of modest fish intake, excepting a few selected species, also outweigh risks.

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Dr. Dariush Mozaffarian obtained his undergraduate degree from Stanford University and his MD from Columbia College of Physicians and Surgeons. He completed his Internal Medicine residency at Stanford University and his Cardiology fellowship at the University of Washington. He also obtained a Masters in Public Health from the University of Washington and a Doctorate in Epidemiology from Harvard. He holds appointments in the Department of Medicine at Harvard Medical School and in the Department of Epidemiology at the Harvard School of Public Health. His primary research interests are the effects of dietary habits on cardiovascular health and disease, including coronary heart disease, sudden death, heart failure, and atrial fibrillation. He has authored numerous original publications on these topics. He is particularly interested in the effects of dietary fats, especially omega-3 fatty acids (found in seafood and plant sources) and trans fatty acids (found in partially hydrogenated oils). He has also elucidated cardiovascular effects of other dietary factors, such as dietary fiber, refined carbohydrates, and saturated fats. His research efforts are funded by multiple grants from the National Institutes of Health.

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