Supplementary Online Content

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eTable 1. Summary of evidence reported in review related to the question: is the high sucrose content of the american diet causally related to CHD?
eTable 2. Studies described in the review by investigators considered threatening by SRF
eTable 3. Arguments that classes of evidence were irrelevant to determining if the high sucrose content of the american diet was a cause of CHD
eTable 4. Summary of evidence reported in the review related to the question: what is the comparative effectiveness of dietary interventions for the prevention of CHD?
eTable 5. Randomized controlled trials of dietary interventions substituting fat or complex carbohydrates for sucrose reported in the review
eTable 6. Randomized controlled trials of dietary interventions reducing dietary cholesterol and substituting polyunsaturated fat for saturated fat reported in the review
eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1: Summary of evidence reported in review related to the question: is the high sucrose content of the American diet causally related to CHD?

Evidence Type	Findings Reported		Arguments that Evidence had no Causal Significance	
	Topic	**Results**	**Individual Studies**	**Classes of Evidence**
Epidemiologic	**Does a Positive Association Exist Between the High Sucrose Content of the American Diet and CHD Morbidity and Mortality Outcomes?**			
	High sucrose intake and CHD Mortality by Country[1,2]	Yes	Investigator incompetence (Yudkin)[3,p188]	Multifactorial confounding precludes identification of dietary causes[4,pp187-188]
	High Sucrose Intake in Developing Countries and Elevated SC[5]	Yes	Poor methodology and data quality (Iowa Group)[3,p188]	
	50 –Year Sucrose Consumption Trends in U.S., U.K. and Increasing CHD Mortality[6,7]	Yes	-	
	Refined Carbohydrate Consumption Trends in Migrating Populations and CHD Mortality[8-10]	Yes	-	
	Sucrose Intake of MI survivors, persons with PAD vs. Controls [11,12]	Yes	Inadequate interpretation (Yudkin)[3,p189]	
Human	**Does Experimental Evidence Show that Sucrose Causes an Elevation in Serum Cholesterol and/or Serum Triglycerides?**			
	Healthy subjects, real-world doses [13-19]	Yes	See Table 2	
	Healthy subjects, semipurified formula diets[20-24]	Yes	-	Experimental conditions irrelevant to real-world: synthetic diets; maximal dose; short duration, effect may be transient.[3,pp191-192]
	Hypertriglyceridemic subjects[25-27]	Yes	Poor data quality, inadequate interpretation (Kuo)[4,pp242-243]	Results not generalizable and do not support biological plausibility[4,pp243-246]
Animal	Controlled Studies in Rats, Chicks, Guinea Pigs[28-37]	Yes	-	Experimental conditions irrelevant to real-world: abnormal dietary cholesterol level required to demonstrate effect; maximal dose; effects achieved with rare low-fat diet; animal models cannot be extrapolated to man; maximal dose; effect may be transient [4,pp243-246]
	Is the Association Biologically Plausible?			
	Mechanistic evidence sucrose has negative metabolic effects on serum cholesterol and serum triglycerides [38-54]	Yes	-	Experimental conditions irrelevant to real-world: maximal dose; used fructose or glucose only; animal models cannot be extrapolated to man;[4,pp243-246]

eTable 2: Studies described in the review by investigators considered threatening by SRF		
Citation	**Findings reported**	**Arguments that evidence was of low quality**
Positive association between high sucrose intake and high CHD mortality by country		
Yudkin, 1957[1] Yudkin, 1964[2]	"Yudkin believes that practically the same data [analyzed by Jolliffe and Archer[55]] support a closer association between the intake of sugar and mortality [than the association between saturated fat intake and mortality]. Suffice it to say that the correlation between the consumption of sugar and saturated fat (r=+0.92) is higher than that between heart-disease mortality and sugar (r=+0.80) or saturated fat (r=+0.82)."[3,p187]	Questioned investigator competence: "Just which of these dietary differences may account for the varying frequency of coronary heart disease cannot be determined by armchair epidemiology."[3,p188]
Positive association between high carbohydrate intake and elevated serum cholesterol in developing countries		
Lopez et al.,1966[5] (The Iowa Group)	"Lopez et al. have utilized ICNND Survey data, collected in various developing countries over the past twenty years, in an attempt to relate the intake of dietary fat and carbohydrate to the level of serum cholesterol in various population groups. Although they interpret these data as showing that serum cholesterol was more closely related to carbohydrates than to fats."[3,p188]	Questioned methodology and data: "Inspection of the ICNND reports simply does not support the validity of this conclusion. Within countries most of the data on food intakes were not calculated for the same population samples in which serum cholesterol was determined; there is a mixture of data from both military personnel and civilians."[3,p188]
Significantly higher sugar consumption in MI survivors and persons with PAD than controls		
Yudkin and Roddy, 1964[2]	"In 1964 Yudkin and Roddy reported in a dietary survey of 3 groups of age-matched men: survivors of a recent myocardial infarction; persons with peripheral vascular disease; and control subjects. Assessment of daily sugar consumption in each of these groups showed the first 2 (average of 132 and 141 gm per day respectively) to be significantly higher than the control group (average of 77 gm. per day)."[3,p189]	Questioned interpretation: "It is interesting that the average sugar intake of the 2 ill groups was about the same as the average per capita consumption in the United Kingdom, which was reported earlier by Yudkin – 139 gm per day. Thus any differences here seem to have been in the curiously low sugar consumption of the control group."[3,p189]
Compared to a self-selected diet, high sugar intake markedly increased serum triglycerides vs. high starch intake when hypertriglyceridemic subjects consumed a moderate fat diet		
Kuo and Basset, 1965[56]	"Kuo and Bassett have reported on the levels of serum lipids and the fatty acid composition of the major lipid moieties in 5 middle-aged subjects with hyperlipidemia and atherosclerosis in response to dietary changes made isocalorically with simple sugar and starch…During the experimental periods of four to six weeks, serum triglycerides were markedly increased in the high sugar and decreased by the high starch – both changes in relation to the self-selected diet. Moreover, the distribution of triglycerides and fatty acids in cholesterol esters showed changes on diets high in sugar compatible with endogenous lipogenesis (increased palmitic, pamitoleic and oleic acid and decreased linoleic acid) but were uninfluenced by the diets high in starch."[4,p242]	Questioned data: "Neither the self-selected comparison diets nor the experimental diets of high sugar or high starch taken for four to six weeks were described in detail. These subjects were apparently maintained on diets providing about 30 per cent of the daily calories from fats. The sources and the nature of the carbohydrates were not mentioned, except for the fact that simple sugar, which comprised 180 to 205 gm. per day on self-selected diets, was increased to 200 to 240 gm. during the period on high sugar. The source of the starch and the types of simple sugars (monosaccharides and disaccharides) were not mentioned. Levels of serum cholesterol which ranged from 250 to 450 mg. per 100 ml. on self-selected diets, were increased in 1 and unaffected in 4 subjects on the diets containing sugar, but were slightly decreased in all subjects on diets high in starch."[4,p242] Questioned interpretation: "This is odd, since the diets high in sugar were very similar to the self-selected diet, whereas the starch diet was quite different."[4p242]

Abbreviations: CHD: coronary heart disease; ICNND: Interdepartmental Committee on Nutrition for National Defense; SC: serum cholesterol; MI: myocardial infarction; PAD: peripheral arterial disease

eTable 3: Arguments that classes of evidence were irrelevant to determining if the high sucrose content of the American diet was a cause of CHD

Types of Evidence	Arguments that Classes of Evidence were Irrelevant	Problems with the Arguments
Population Studies	**Multifactorial confounders precluded the identification of dietary factors causally related to CHD**	
International Dietary Intakes	"What is indicated by inspection of these reports of international dietary intakes is that economic development is associated with more animal protein and saturated fat, more total fat, an increase in simple sugars and a marked decline in the consumption of complex carbohydrates from cereals, grains and vegetables…And when one considers the host of other differences associated with socioeconomic development (decreased physical activity, obesity, addiction to cigarettes, elevated blood pressure and perhaps "stress and strain"), as well as those in the prevalence of coronary heart disease *within* a country, one may see how difficult it is to relate specific dietary factors to atherosclerotic vascular disease."[3,pp187-188]	*From the 1964 Surgeon General's Report, Smoking and Health*: "It is evident that the greater the number of causal agents producing a given disease the less strong and the less specific will be the association between any one of them and the total load of the disease. But this could not be posed as a contradiction to a causal hypothesis for any one of them even though the predictive value of any one of them might be small."[57]
Trend Data	"whether these trends – also accompanied by many other changes in one's way of life—can be uniquely related to the apparently increasing frequency of atherosclerotic disease is a moot point."[3,p188]	
Migrating Populations	"The same problems [as above] underlie meaningful interpretation of data on migrating populations."[3,p188]	
Human	**Experimental conditions cannot be extrapolated to real-world conditions**	
Controlled Studies, Healthy Subjects	<u>Synthetic diets, maximal dose, short duration:</u> "A number of studies using semi-purified formula diets, in which variations in type and level of carbohydrates can be more extreme, have been reported. It should be clear that such studies even tough they demonstrate dietary effects, do not implicitly reveal knowledge of practical applicability or usefulness for the general population."[3,p191]	*From Mann and Stare's 1954 presentation to the NAS-NRC arguing that atherosclerosis should be managed by reducing total calories and total fat:* "The manipulation of time and intensity variables can hardly be used has evidence that the experiments are invalid." [58,p173]
	Effect of sucrose on elevating serum triglycerides in humans may be transient	
	"Since Antonis and Bersohn have shown that the serum triglyceride response to the feeding of a diet low in carbohydrate is a transient rise, with a gradual diminution over time, the results of short-term feeding trials must be interpreted with caution."[3,pp191-192]	*From Antonis and Bersohn's Original Publication:* "In view of recent work which indicates a close relation between hyperlipaemia and accelerated blood-clotting and decreased blood-fibrinolyitic activity, the production of even temporary lipeaemia may be inadvisable in ischaemic-heart disease patients."[59,p9]
Controlled Studies, Hyper-triglyceridemic Subjects	**Results not generalizable to American public**	
	"On the other hand, [Kuo] was unable to raise the serum triglyceride levels in young men in whom the daily sucrose intake was approximately doubled."[4,p242]	The review implied that widespread CHD interventions should be designed based on how a typical healthy American responded to them.

eTable 3: Arguments that classes of evidence were irrelevant to determining if the high sucrose content of the American diet was a cause of CHD

Types of Evidence	Arguments that Classes of Evidence were Irrelevant	Problems with the Arguments
	Results do not support biological plausibility	
	"Limited studies comparing a fructose with a sucrose diet led Kuo to conclude that fructose has a 'low lipemic effect as compared to sucrose'…Thus, these studies on subjects with gross hypertriglyceridemia, although possibly confirming the previously described carbohydrate effects have raised other issues…Kuo's studies with fructose may cast some doubt on the idea usually advanced that fructose yielded by the hydrolysis of sucrose is responsible for the hypertriglyceridemia."[4,pp242-243]	*From Kuo's Original Publication, both fructose and sucrose are lipogenic:*"The possibility that fructose, a constituent of sucrose, but not of starch, is the lipemic agent was studied in three of the hyperglyceridemic patients…[In one patient] substituting fructose for the starch calories caused a recurrence of hyperglyceridemia with an intensity comparable to that produced by the high sucrose diet, but did not result in significant elevations in the serum phospholipid and cholesterol levels of the patient. In comparison with the serum lipid values observed in two other hyperglyceridemic patients during the high sucrose diet period, fructose feeding appeared to produce relatively mild degrees of hyperglyceridemia in both patients."[25]
Animal Experimentation	**Experimental conditions cannot be extrapolated to real-world conditions**	
Controlled Studies	<u>High levels of dietary cholesterol were required to demonstrate an effect of dietary factors on serum cholesterol:</u> "Elevation of the level of serum cholesterol produces vascular lesions of varying similarity to human atherosclerosis in nearly all animal species that have been studied. Several recent reviews are available on the manipulations, including dietary, that have been used to initiate and to accelerate the development of such vascular lesions. For the most part, unfortunately, most of these studies have dealt with diets containing large amounts of cholesterol, amounts far greater, in proportion to size, than those consumed by man. Much less is known of the influence of various kinds of fatty acids in diets incorporating little or no exogenous cholesterol. The question may be raised whether studies done with diets heavily supplemented with dietary cholesterol, or the effects of various dietary modifications of such diets, can be meaningfully interpreted in terms of human nutrition. In our opinion, most of the studies reported with such diets have little significance, especially those done with rats, whose response in serum cholesterol to dietary fat and cholesterol is markedly different from that of man."[4,p243]	*From Mann and Stare's 1954 presentation to the NAS-NRC arguing that atherosclerosis should be managed by reducing total calories and total fat***:** "We cannot accept [the] dismissal of cholesterol-feeding experiments in animals on the basis that the amount of cholesterol fed in order to induce experimental disease is out of all proportion to what a human being would consume. The experimentalist is attempting, for reasons of expediency, to accelerate a process which in natural circumstances is so slow that study is virtually impossible." [58,p173]
	<u>Maximal dose:</u> "Finally, it should be borne I mind that diets administered to these animals, in addition to being low in fat and very high in carbohydrate, also represent maximal changes in the dietary carbohydrate – all	*From Mann and Stare's 1954 presentation to the NAS-NRC arguing that atherosclerosis should be managed by reducing total calories and total fat:* "The manipulation of time and intensity variables can hardly be used has evidence that

eTable 3: Arguments that classes of evidence were irrelevant to determining if the high sucrose content of the American diet was a cause of CHD

Types of Evidence	Arguments that Classes of Evidence were Irrelevant	Problems with the Arguments
	starch or all sugar. These diets should have the greatest metabolic effects but probably have limited significance when compared with the more moderate changes possible under ordinary conditions in diets for man." [4,p244]	the experiments are invalid or that cholesterol is an artifact to the problem of atherosclerosis" [58,p173]
	Humans rarely consume low-fat diets: For reasons that are not clear, diets given to rats are traditionally low in fat. Thus, the response of rats, as of man, to diets high in sugar and low in fat may be thought to be of limited significance since such diets are rarely consumed by man."[4,p244]	No evidence was cited to support this statement.
	Interspecies variation precludes comparison of animal models to man	
	"Effort is needed to identify species whose response in serum lipids to dietary modifications is similar to that seen in man." [4,p243] "An evaluation of the significance of these findings in animals in relation to the problem of hypercholesterolemia and atherosclerosis in man does not seem possible at present."[4,p244] "In addition, the question arises whether the hypercholesterolemic rat is sufficiently similar to hypercholesterolemic man to serve as a useful model. It has been demonstrated that the response of such animals to variations in the kind of dietary fat has little similarity to that seen in man. When a wide variety of fats were tested in such animals, the highest levels of serum cholesterol were found with olive oil, and it appears that monounsaturated fatty acids tend to elevate levels of serum cholesterol above those seen with either more saturated or less saturated oils. This is contrary to all data available on man."[4,p244]	*From Mann and Stare's 1954 presentation to the NAS-NRC arguing that atherosclerosis should be managed by reducing total calories and total fat*: **"**The study of laboratory animals of various species subjected to feeding regimens is the most informative approach to an understanding of atherosclerosis. It is in this situation, permitting adequate control of variables, that efficient experimentation can be done. It is well to be aware of the extreme species variations which exist in respect to cholesterol metabolism, to natural serum lipid patterns, and to the susceptibility of vascular tissue to atherosclerotic changes." [58,p173] "Cholesterol feeding is an extremely useful tool for the production and study of experimental hypercholesterolemia, hyperlipoproteinemia, and several forms of atherosclerosis in experimental animals. The several useful experimental species vary both according to serum and tissue response to cholesterol feeding. Standard methods of experimental nutrition will control much of this variability, and interspecies variability should be turned to advantage by comparative studies." [58,p176]
	Effect of sucrose on elevating serum triglycerides in animals may be transient	
	"In view of the fact that Antonis and Bersohn found that the adaption of their subjects to diets high in carbohydrate required a substantial time, and Fillios et al have provided evidence that similar adaption may occur in rats, most of the data on laboratory animals obtained with relatively short experimental periods may represent a temporary adjustment to the diets given."[4,p244]	*From Antonis and Bersohn's Original Publication:* "In view of recent work which indicates a close relation between hyperlipaemia and accelerated blood-clotting and decreased blood-fibrinolyitic activity, the production of even temporary lipeaemia may be inadvisable in ischaemic-heart disease patients."[59,p9]
Mechanistic Studies	**Experimental conditions cannot be extrapolated to real-world conditions**	
	Maximal dose: "When the effects of specific	*From Mann and Stare's 1954 presentation to the*

eTable 3: Arguments that classes of evidence were irrelevant to determining if the high sucrose content of the American diet was a cause of CHD		
Types of Evidence	**Arguments that Classes of Evidence were Irrelevant**	**Problems with the Arguments**
	carbohydrates have been investigated, the investigators for obvious reasons have usually compared diets in which all the carbohydrate is from one source. The effects observed are thus presumably maximal. Under practical conditions, the major source of fructose will be from sucrose mixed with other carbohydrate sources yielding primarily glucose upon hydrolysis. It is thus uncertain how far the findings can be extrapolated."[4,p244]	*NAS-NRC arguing that atherosclerosis should be managed by reducing total calories and total fat:* "The manipulation of time and intensity variables can hardly be used has evidence that the experiments are invalid."[58,p173]

eTable 4: Summary of evidence reported in the review related to the question: what is the comparative effectiveness of dietary interventions for the prevention of CHD?

Evidence Type	Sucrose Findings Reported				Arguments that a Sucrose Intervention *Would Not Be* Effective			Conclusion
	Population	**Intervention**	**Outcome**	**Effect Size**	**Outcome**	**Feasibility**	**Coherence of Evidence**	
Human Experimental	**Evidence of the effectiveness of modifying the high sucrose content**							
	Healthy subjects[16]	Substituting fat for sucrose	Serum Triglycerides	Large	Irrelevant[3,p187]	Low[4,p247]		Substituting the high sucrose content of the American diet with fat and/or complex carbohydrates is not likely to be of benefit in the prevention of CHD[4,pp246-247]
	Hyper-triglyceridemic subjects[25-27]	Substituting starch for sucrose	Serum Triglycerides	Large	Irrelevant[4,p242]			
	Healthy subjects[13-15]	Substituting leguminous vegetables for sucrose	Serum Cholesterol	Large		Low[3,p191]		
	Healthy subjects[17-19]	Substituting starch for sucrose	Serum Cholesterol	Small		High but small effect indicates low effectiveness[3,p191]	Low[4,p246]	
Evidence Type	**Fat Findings Reported**				**Arguments that a Fat Intervention *Would Be* Effective**			**Conclusion**
	Population	**Intervention**	**Outcome**	**Effect Size**	**Outcome**	**Feasibility**	**Coherence of Evidence**	
Human Experimental	**Evidence of the effectiveness of modifying the high saturated fat content of the diet**							
	Healthy subjects[60-64]	Reducing dietary cholesterol and substituting polyunsaturated for saturated fat	Serum Cholesterol	Large	Most relevant[4,p246]	High[4,p246]	High[3p190,4,p246]	Reducing dietary cholesterol and substituting polyunsaturated fat for saturated fat are the changes to the American diet most likely to be of benefit to prevent CHD[4,pp246-247]

eTable 5: Randomized controlled trials of dietary interventions substituting fat or complex carbohydrates for sucrose reported in the review

Findings Reported				Arguments that Interventions Would Not Be Effective	Problems with the Arguments
Population	**Intervention**	**Outcome**	**Effect Size**		
Healthy subjects[16]	Substituting fat for sucrose	Serum Triglycerides	Large	**Serum triglycerides not a relevant outcome to measure effectiveness of dietary interventions**	
				"The major evidence today suggests only one avenue by which diet may affect the development and progression of atherosclerosis. This is by influencing the levels of serum lipids, especially serum cholesterol, though this may take place by means of different biochemical mechanisms not yet understood."[4,p246]	*From review introduction:* "It has only been in the past decade that several prospective epidemiologic studies have demonstrated the clear and quantitative association between the level of certain blood lipids and the subsequent incidence of coronary and thrombotic vascular disease. It is certainly true that serum cholesterol has received by far the most attention in the pathogenesis of atherosclerotic vascular disease. The main reasons for the relative deficit in the knowledge of distributions of the levels of serum triglycerides or of the several lipoprotein classes in various population groups can be considered as much the difficulty of obtaining fasting bloods in many kinds of studies as the more cumbersome analytical technics required."[3,p187]
				"two prospective studies have failed to demonstrate convincingly that foreknowledge either of lipoprotein levels or of triglycerids provides better predictors of clinical disease than serum total cholesterol itself."[3,p187]	*From Brown et al's original publication:* "Fifty-six subjects acquired ischemic heart disease during the four-year period after the triglyceride level was measured. The disease occurred more frequently in association with increasing levels of either cholesterol or triglyceride. Although there was a suggestion that triglyceride elevation might have an independent effect on incidence the small number of subjects made it impossible to confirm this point."[65]
				Intervention has low feasibility	
				"diets low in and high in sugar are rarely taken."[4,p247]	No evidence was cited to support this statement
Hyper-triglyceridemic subjects[25-27]	Substituting starch for sucrose	Serum Triglycerides	Large	**Serum triglycerides not a relevant outcome to measure effectiveness of dietary interventions**	
				"So-called hyperlipidemias, for which Fredrickson et al. have provided a useful classification, in effect are usually applied to persons representing the upper 5 per cent or 10	*From review results:* "On the other hand, there is evidence that patients with the Type 4 abnormality – carbohydrate-inducible hypertriglyceridemia—do show an exaggerated response to changes in the

eTable 5: Randomized controlled trials of dietary interventions substituting fat or complex carbohydrates for sucrose reported in the review

Findings Reported				Arguments that Interventions Would Not Be Effective	Problems with the Arguments
Population	**Intervention**	**Outcome**	**Effect Size**		
				per cent of the general population (Fig 1 and Table 1). The widespread prevalence of atherosclerosis and its clinical complications in developed societies and a broader view of blood lipid distributions in various populations, including the age-related increase in American society, suggest that most middle-aged American men have hypercholesterolemia and probably hypertriglyceridemia as well. If one is to think in terms of dietary changes with the reasonable idea of preventing or retarding atherosclerotic vascular disease, there is no reason at all to restrict such efforts to a small segment of a susceptible population."[4,p242]	absolute quantity as well as to the type of dietary carbohydrate." *From Albrink's original publication (known to SRF and review authors but omitted from review):* "In recent years the pendulum of opinion regarding the etiology of atherosclerosis has swung away from the mechanistic view that ingested fat and cholesterol merely find their way through the blood stream to the arterial wall, toward the concept of an underlying metabolic abnormality. Growing evidence suggests that an important and perhaps basic dfect is in the area of carbohydrate metabolism…The association between impaired carbohydrate metabolism and atherosclerosis reported by Ostrander and associates and between dietary carbohydrate and hypertriglyceridemia reported by Kuo and Bassett are consistent with hypotheses that the common modern diseases of diabetes, atherosclerosis, and obesity and associated hyperglyceridemia may be the present day manifestations of the effect of affluence on a once useful genetic trait, the ability to conserve carbohydrate."[66]
Healthy subjects[13-15]	Substituting leguminous vegetables for sucrose	Serum Cholesterol	Large	**Intervention has low feasibility**	
				"In summary, these controlled studies, which have all used carbohydrate variations within practical and palatable ranges of intake, and have included ordinarily available foodstuffs, have demonstrated slight reductions in blood lipids when dietary simple sugars are replaced by complex carbohydrates. However, these changes are of such a small order as compared with those obtained by changes in fats that in our opinion they have no practical importance. That the carbohydrates in leguminous vegetables may be more efficient than those in potatoes and	The review implied that replacing sucrose with leguminous vegetables was not feasible. No evidence was cited to support this inference.

eTable 5: Randomized controlled trials of dietary interventions substituting fat or complex carbohydrates for sucrose reported in the review

Findings Reported				Arguments that Interventions Would Not Be Effective	Problems with the Arguments
Population	**Intervention**	**Outcome**	**Effect Size**		
				cereals in this regard suggests that undefined factors may be involved."[3,p191]	
Healthy subjects[17-19]	Substituting starch for sucrose	Serum Cholesterol	Small	**Intervention is feasible, but would have minimal effectiveness compared to a fat intervention**	
				See above.	The review implied that the only feasible intervention was replacing sucrose with starches sweetened with artificial sweeteners. No evidence was cited to support this inference.
				Low Coherence of Evidence	
				"Limited evidence from studies on man as well as from researches on laboratory animals show a slightly significant role for the kind and amount of dietary carbohydrate in the regulation of serum lipids."[4,p242]	Evidence was limited because the review had discounted the majority of studies.

eTable 6: Randomized controlled trials of dietary interventions reducing dietary cholesterol and substituting polyunsaturated fat for saturated fat reported in the review

Findings Reported				Arguments that Fat Intervention Would be Effective	Problems with the Arguments
Population	**Intervention**	**Outcome**	**Effect Size**		
Healthy subjects[60-64]	Reducing dietary cholesterol and substituting polyunsaturated fat for saturated fat	Serum Cholesterol	Large	**Serum cholesterol should be the only target of dietary interventions**	
				"The major evidence today suggests only one avenue by which diet may affect the development and progression of atherosclerosis. This is by influencing the levels of serum lipids, especially serum cholesterol, though this may take place by means of different biochemical mechanisms not yet understood."[4,p246]	*From review introduction:* "It has only been in the past decade that several prospective epidemiologic studies have demonstrated the clear and quantitative association between the level of certain blood lipids and the subsequent incidence of coronary and thrombotic vascular disease. It is certainly true that serum cholesterol has received by far the most attention in the pathogenesis of atherosclerotic vascular disease. The main reasons for the relative deficit in the knowledge of distributions of the levels of serum triglycerides or of the several lipoprotein classes in various population groups can be considered as much the difficulty of obtaining fasting bloods in many kinds of studies as the more cumbersome analytical technics required."[3,p187] *From review results:* "On the other hand, there is evidence that patients with the Type 4 abnormality – carbohydrate-inducible hypertriglyceridemia—do show an exaggerated response to changes in the absolute quantity as well as to the type of dietary carbohydrate." [4,p242]
				Fat intervention is highly feasible	
				"The solution here, in our opinion, is a responsibility and opportunity for the food industry – namely, the manufacture of many common foods with characteristics that will lessen the development of atherosclerosis. This is possible today and only awaits leadership from the food industry."[4,p246]	The intervention was feasible, but may not achieve the desired result.
				RCTs tested and recommended equivalent interventions	

eTable 6: Randomized controlled trials of dietary interventions reducing dietary cholesterol and substituting polyunsaturated fat for saturated fat reported in the review

Findings Reported				Arguments that Fat Intervention Would be Effective	Problems with the Arguments
Population	**Intervention**	**Outcome**	**Effect Size**		
				"That the magnitude of the responses in blood lipids to the kinds of dietary manipulations described above [by Antonis and Bersohn][59,60] are due almost entirely to the effects of dietary fats has been amply confirmed by Keys, Ahrens, Kinsell and Hegsted. The chain length and the degree of saturation of the fatty acids in the dietary fat and the quantity of dietary cholesterol can account for essentially all the observed changes in closely controlled studies involving manipulations in the type and amount of dietary fat."[3,p190]	*Varied interventions recommended in original RCT publications:* Ahrens: Replace saturated fats with "highly unsaturated oils" based on "the degree of saturation of the glyceride fatty acids as measured by the iodine value of the fat."[62] Kinsell: "The addition of purified ethyl and glycerol esters of linoleic acid [essential fatty acid] to the diet" [63] Keys: "a decrease in the most common fats in [the American and Western European diets] and the secondary substitution of fats high in polyethenoid fatty acids." (Iodine value is not useful to identifying healthy/unhealthy fats, no evidence that adding linoleic to the diet is effective)[61] Hegsted: "Eat a diet relatively high in total fat with (a) a small proportion of myristic and palmitic acids, particularly myristic acid; (b) a high proportion of polyunsaturated acids; and (c) a small amount of dietary cholesterol."[64]
				RCTs are coherent with epidemiologic evidence	
				"We conclude, on the basis of epidemiologic, experimental and clinical evidence, that a lowering of the proportion of saturated fatty acids, increasing the proportion of polyunsaturated acids and reducing the level of dietary cholesterol are the dietary changes most likely to be of benefit."[4,p246]	*From review results re: epidemiologic evidence:* [There are] obvious limitations of international epidemiologic studies. Even with data from the very carefully carried out studies by Keys et al., it may be impossible to ascribe population differences in blood lipids and morbidity or mortality from coronary heart disease to dietary practices alone."[3,p188]
				RCTs are confirmed by clinical evidence	
				From review results re: clinical evidence, cited preliminary results: "Clearly needed now are	*From Leren's original publication, fat intervention group restricted sugar intake against advice:* "Diet

eTable 6: Randomized controlled trials of dietary interventions reducing dietary cholesterol and substituting polyunsaturated fat for saturated fat reported in the review

Findings Reported				Arguments that Fat Intervention Would be Effective	Problems with the Arguments
Population	Intervention	Outcome	Effect Size		
				the longitudinal clinical trials designed to show whether or not a group of individuals who have achieved a reduction in serum cholesterol through dietary manipulation will also manifest a reduced risk of clinical atherosclerotic vascular disease. To carry out such a study beginning with healthy, middle-aged men, properly randomized into treatment and control groups, and followed up for the development of coronary heart disease, is a truly formidable undertaking. The nature of these problems is outlined in the preliminary report of the National Diet-Heart Study group." "Nevertheless, the most recent report from the Anti-Coronary Club in New York City does suggest a significant reduction in the incidence of coronary heart disease in a group of men whose average level of serum cholesterol was reduced by 12 percent on a diet restricted in saturated fats and cholesterol while increased in polyunsaturated fat." "Another approach has been used in Oslo by Leren, who has reported a five-year follow-up study of 412 male survivors, thirty to sixty-seven years of age, of a documented myocardial infarction. These men were randomly assigned to a dietary treatment and a control group. Goals of the dietary instruction were similar to those in the New York city study. The serum cholesterol levels was reduced by 17 per cent in the treatment group, an effect maintained over the five years ot the study. Over the five-year period of observation, 34 of the treatment group had 43 new myocardial infarctions (10 fata); 54 of the control group had 64 new infarctions (23 fata). Furthermore, 10 of 75 patients in the dietary group who were initially without angina pectoris	changes achieved in the diet group…. abundant use of marmalade, jam, fruit, juice, etc. had been recommended. Nevertheless, sugar consumption is low."[67,p31]

eTable 6: Randomized controlled trials of dietary interventions reducing dietary cholesterol and substituting polyunsaturated fat for saturated fat reported in the review

Findings Reported				Arguments that Fat Intervention Would be Effective	Problems with the Arguments
Population	Intervention	Outcome	Effect Size		
				subsequently manifested this syndrome; the rate was 29 of 79 in the control group. If confirmed by other studies, this report represents a signal advance in the ability to control the major cause of disability and death in contemporary Western societies."[4, p243]	
				Lack of mechanistic evidence unimportant	
				"The major evidence today suggests only one avenue by which diet may affect the development and progression of atherosclerosis. This is by influencing the levels of serum lipids, especially serum cholesterol, though this may take place by means of different biochemical mechanisms not yet understood."[4,p246]	Mechanistic evidence supported the biological plausibility that sucrose raised serum cholesterol and serum triglycerides.

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