VARIANCE AND DISSENT
Presentation

A hypothesis out-of-date: The diet–heart idea

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Abstract

An almost endless number of observations and experiments have effectively falsified the hypothesis that dietary cholesterol and fats, and a high cholesterol level play a role in the causation of atherosclerosis and cardiovascular disease. The hypothesis is maintained because allegedly supportive, but insignificant findings, are inflated, and because most contradictory results are misinterpreted, misquoted or ignored. © 2002 Elsevier Science Inc. All rights reserved.

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1. Introduction

The idea that an imbalance of dietary cholesterol and fats, and high serum cholesterol, are the primary cause of atherosclerosis and cardiovascular disease, the diet–heart hypothesis, has dominated our thinking for many decades. The diet–heart hypothesis is generally considered to be based on solid scientific evidence. However, when I reviewed the epidemiologic and experimental studies of the direct link between dietary fats and cardiovascular disease I found that almost all studies were inconclusive or, indeed, flatly contradictory. Most important, perhaps, is the fact that not a single life has been saved by experimental manipulation with dietary fat [1].

According to Kuhn [2], a scientific theory is declared invalid only if an alternate candidate is available. In the meantime, all anomalies are met by manipulations and ad hoc modifications compounded by science students who accept theories on the authority of teacher and text, without analyzing the evidence, critically, for themselves.

This situation is a normal part of science, and may have little importance if the hypothesis in question has theoretical interest only. But the diet–heart hypothesis has had a massive impact on preventive health care, medical research, food production, and the private life of millions of people all over the world. Evidently, a retraction is difficult because much prestige and money has been invested. But to prevent biased thinking we need to look at the evidence with an objective and open mind.

2. The diet

Below I have summarized the strongest contradictory findings from my review, mentioned above, in order of increasing scientific strength. A complete reference list is given in the review [1].

2.1. Ecologic and dynamic population studies

No consistent associations were found in ecologic studies between the consumption of saturated fatty acids (SFA) or the total fat consumption, and coronary mortality in various countries. Using data from the Food and Agriculture Organization of the United Nations and the World Health Organization, Keys did find an almost perfect positive, curvilinear correlation between the total fat consumption and coronary mortality in six countries [3]. However, in an attempt to reconstruct Keys' diagram, Yerushalmy and Hilleboe found the correlation trivial [4]. The reason was that Keys had excluded data from 16 countries that did not fit the hypothesis.

Many authors have claimed support from dynamic population studies that included figures from a single country only. In four studies that included the results from 18–35 countries [1,5–7], secular trends of saturated fat consumption and secular trends of coronary mortality followed each other in 41 of 103 time periods in 35 countries. However, in 13 time periods an increased consumption was not followed by an increased coronary mortality, and in 28 time periods the secular consumption and mortality trends went in opposite directions [1].

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2.2. Cross-sectional studies

Authors from numerous cross-sectional studies have claimed support for the diet–heart idea, but most of them have not included a control or comparison population. When cross-sectional studies that included a control group were considered only, one group of studies was supportive, six groups of studies gave partly supportive, partly contradictive results, in seven groups of studies the findings were contradictive [1]. In the following I have included the most spectacular contradictory studies only.

Results from the Japanese migrant studies are often referred to as supportive of the diet–heart hypothesis. It is said that when Japanese people, known for their low cholesterol and their low mortality from coronary heart disease (CHD), migrate from Japan where the food is lean, to the United States where the food is much fatter, their cholesterol and their coronary mortality rise to American levels. What is rarely mentioned is that the decisive factor for the migrants' coronary mortality was their cultural upbringing, not their diet or cholesterol. Those who adhered to Japanese traditions after migration kept their low risk of CHD independently of what they ate. In fact, migrants, who were brought up in a nontraditional fashion but preferred the lean Japanese food had almost twice as much CHD than those who were brought up traditionally but preferred American food [8].

Comparative postmortem studies of Americans and Japanese are also contradictory. Despite their low cholesterol, Japanese people have just as much atherosclerosis as Americans [9], if not more [10].

Several African tribes live mainly on camel or sebu milk, which is much fatter than that from Holstein cows, the dominating source of milk in the United States. Despite that, their cholesterol is much lower than the average American, and cardiovascular diseases are rare. Masai people, for instance, who consumed twice as much SFA than the average American had fewer pathologic electrocardiographic findings than age- and sex-matched Americans, and complicated atherosclerotic lesions were rare [11,12].

The most remarkable falsification of the diet–heart idea based on a cross-sectional study comes from India. In a study of more than one million railway workers CHD mortality was seven times higher in South India than in Punjab, and mean age at death from CHD was 44 in South India and 52 in Punjab, although people from Punjab ate 19 times more fat, mostly of animal origin, and also smoked more [13].

2.3. Case–control studies

Comparisons of the diet of CHD patients and matched control individuals are difficult because many patients with CHD alter their diet following diagnosis. However, six available case–control studies of patients with CHD or peripheral atherosclerosis were published between 1959 and 1974, long before dietary prevention became routine. No significant difference was found in these studies between the consumption of SFA or polyunsaturated fatty acids (PUFA) in the patients and the healthy control individuals [1].

In four case–control studies of atherosclerosis at autopsy, the degree of postmortem atherosclerosis was unrelated to SFA and PUFA consumption. In one of the studies, atherosclerosis was positively correlated with the total fat consumption, in another one negatively, in two studies no correlation was found [14–17].

2.4. Cohort studies

The above-mentioned bias is less likely in cohort studies because information about the diet is achieved before the heart attack. In 21 cohort studies of CHD including 28 cohorts with more than 150,000 individuals, no study found a consumption pattern of SFA and PUFA that was in accordance with the diet heart hypothesis [1].

Since the publication of my review, two more large cohort studies have been published. In one of them, no difference was found between SFA and PUFA consumption, but CHD patients had a significant lower dietary ratio of PUFA/SFA than non-CHD individuals [18]. While this would appear to support the diet–heart hypothesis, in the other study, CHD patients had eaten significantly more PUFA and significantly less SFA [19].

2.5. Trials

The definitive test for causality is the controlled, randomized clinical trial. In a meta-analysis of nine such trials, where the only intervention was to alter dietary fat consumption (to a much greater degree than recommended by any health authority), coronary and total mortality was unchanged [1]. In the only trial with a significant reduction of mortality in the treatment group, serum cholesterol was identical in both groups, and its positive effect was balanced by another trial with a nearly significant increase of mortality in the treatment group.

Recently, another meta-analysis of the dietary trials was published, again demonstrating no effect on CHD and total mortality. However, in a subgroup analysis, trials where participants were involved for more than 2 years on average had a significant reduction for the rate of combined cardiovascular events in the treatment group that made the authors conclude that their meta-analysis supported "a central role of dietary fat intake in the causation of cardiovascular disease" [20]. To reach that conclusion the authors had included a trial that was biased by a significantly higher number of heavy smokers in the control group. In addition, the authors excluded the trial with the most contradictive result [21].

2.6. Dietary cholesterol

For many years, health authorities have recommended a reduction in cholesterol intake. This is most curious because numerous studies have found little or no influence of dietary

cholesterol on blood cholesterol [22,23]. It has been argued that the small mean changes of blood cholesterol seen after high intakes are biased because some individuals are low responders, others are high responders. This is not in accordance with available evidence. In response to a 2-week high-cholesterol diet, about 25% of 94 test individuals were classified as hyperresponders and about 20% as low responders. However, when the experiment was repeated, no difference was found between these two groups, and in a third experiment with the same test individuals using a much higher cholesterol intake, some of those who were hyperresponders in the first test had become hyporesponders [24,25].

In addition, there is no epidemiologic evidence that a high intake of cholesterol has any effect on CHD risk. As seen from Table 1, none of 13 cohort studies [18,19,26–36], including more than 190,000 individuals, found a significant difference between the dietary intake of cholesterol in those with, or without, CHD at follow-up.

2.7. Monounsaturated fatty acids (MUFA)

At least nine cohort studies have compared the intake of MUFA between those who had CHD at follow-up and those who had not [18,19,28–31,34,35,37]. None of the studies supported the hypothesis that this group of fatty acids can protect against CHD (Table 1). In fact, two studies found that patients with CHD at follow-up had eaten significantly more MUFA than non-CHD individuals [34,35]. Hu et al. [38] argued that a possible protective effect of MUFA may remain undetected because dietary MUFA mainly comes from food items that also contain much SFA. If their explanation were correct, the ratio between SFA and MUFA consumption should be higher in patients than in controls. Table 1 shows

Table 1
Daily average intake of monounsaturated fatty acids and of cholesterol, and the ratio between SFA and MUFA consumption in CHD patients and CHD-free individuals in 13 cohort studies of 191,157 individuals free of CHD at baseline

	Number of individuals; CHD/no CHD	Observation time; years	MUFA (percent of total energy consumption) CHD/no CHD	Ratio SFA/MUFA CHD/no CHD	Cholesterol; (mg/day) CHD/no CHD	Adjustments in separate regression models, or similar
Paul *et al.* [26]	88/1797	4	—	—	721/757	Bp,bw,pr
Kannel and Gordon [27]						a
men	32/380	16	—	—	708/716	
women	15/419				520/477	
Garcia-Palmieri *et al.* [28]		6				a
urban	213/5585		14.5/14.5	0.94/0.90	449/442	
rural	73/2347		13.3/13	0.98/0.97	333/358	
Gordon *et al.* [29]						a
Framingham	79/780	4	16.3/15.8	0.94/0.94	534/529	
Puerto Rico	286/7932	6	14.2/13.9	0.95/0.96	419/417	
Honolulu	264/7008	6	13.4/12.8	0.95/0.96	549/555	
McGee *et al.* [30]	456/6632	10	13.6/12.8	0.93/1.04	558/552	a,bp,bw,c,p,sm
Kromhout & Coulander [31]	30/827	10	18.5/18.2	0.96/0.97	446/429	a,bw,c
Kushi *et al.* [32]	110/891		—	—	854/832	a,al,bp,c,e,sm
Khaw & Barret-Connor [33]						
men	42/314		—	—	470/409	a,bp,bw,c,d,sm
women	23/480				226/309	
Posner *et al.* [34]						
45–55	99/321	16	CHD>no CHD**	See text	ns	a,bp,bw,c,d,e,
>55 år	114/279		ns		ns	Fat,p
Esrey *et al.* [35]						
30–59	52/3873	12	16.9/15.5ª	0.99/0.97	427/416	a,bp,bw,c,d,sm
60–79 år	40/581		15.1/14.7	0.91/0.97	423/355	
Ascherio *et al.* [36]	734/43757		—	—	ns	a,al,bp,c,f,fa,p, pr,sm
Pietinen *et al.* [19]	1,399/21930	6	ns	See text	ns	bp,bw,c,f,fat,p,pr,sm
Hu *et al.* [18]	281/79801	14	ns	See text	ns	ac,bp,bw,fa, me,p,sm,v
Farchi *et al.* [37]	58/1263	15	14.9/15.9	0.54/0.57	—	a
Total	4,400/187,197					

*P<.05; **P<.01; ns = not significant; a = age; al = alcohol; bp = systolic blood pressure; bw = body weight or other indices of obesity b = blood cholesterol and/or other blood lipids; d = diabetes; f = fiber intake; fa = family history; fat = other fats; me = menopause; p = physical activity; pr = profession; r = race; sm = smoking; v = vitamin use.

that the differences in the cohort studies were trivial; in fact, the ratio was lower in six studies and higher in only three studies. In a further three studies [18,19,34] it was not possible to calculate this ratio from the data given, but the figures for MUFA consumption in these studies were correlated for intake of SFA (Table 1).

3. Role of high cholesterol

The lack of evidence for a causal role of dietary cholesterol and saturated fat, and a protective role of polyunsaturated fat points to a dilemma. As there is no doubt that an excess of saturated fat may raise cholesterol and an excess of polyunsaturated fat may lower it, at least in laboratory experiments, how is it that such dietary changes do not prevent cardiovascular disease? The answer may be that high cholesterol is a risk marker of CHD, not a cause. Below, I have laid out some of the most crucial findings that support this view. (As the number of such studies is enormous, I have referred to a few illustrative examples only; an exhaustive reference list is given elsewhere [39].)

3.1. Cohort studies

It is generally believed that a high cholesterol is a strong predictor for future CHD. However, there are many exceptions to the rule. In women, many studies have demonstrated that high cholesterol levels do not predict CHD risk [1]. A review of 11 cohort studies, including more than 120,000 women, found an increased risk for coronary mortality in the fourth cholesterol quartile only (RR 1.56), whereas the risk for all cardiovascular and for total mortality was independent on the cholesterol level [40]. In men, there are many populations where a high cholesterol level is not predictive of CHD either [1,41]. In Framingham, for example, a decreasing cholesterol level predicted an increased risk of CHD and total mortality. For each 1 mg/dL drop of cholesterol there was an 11% increase in coronary and total mortality [42]. In a Russian study, *low* cholesterol predicted CHD and total mortality [43]. In almost all studies high cholesterol does not predict CHD in the elderly [42,44]. Indeed, the higher the cholesterol level, the lower the risk [45,46]. Finally, in most studies high cholesterol does not predict a new heart attack in patients with manifest CHD [1,47].

3.2. Cross-sectional studies

The number of cross-sectional studies of serum cholesterol in various populations and patient groups is almost endless. The following examples only provide a sample of the most contradictory observations.

In almost all postmortem studies the degree of atherosclerosis was independent of blood cholesterol [48,49]. A few studies have found a weak, positive correlation, but they have been biased by including patients with familial hypercholesterolemia (FH). After exclusion of such patients the correlation disappeared [1].

No angiographic study has found a correlation coefficient above 0.36 between serum cholesterol and the degree of coronary atherosclerosis. In most cases the correlation is even less powerful, or absent [50,51]. Again, the correlation found is most probably due to the fact that most angiographic studies include a substantial number of patients with FH, which will bias the results. There is no correlation, either between low-density lipoprotein (LDL) cholesterol or total cholesterol, and degree of atherosclerosis in this patient group either [52], but if a study includes both FH and non-FH patients, a false correlation may be created because even if degree of atherosclerosis is unassociated with the cholesterol level in both groups, patients with FH have generally higher cholesterol and more atherosclerosis.

Finally, it is a striking fact that several family units of individuals with FH have had a lower than normal CHD and total mortality than the general population [53]. Obviously, it is other factors than the high cholesterol that give rise to the vascular changes in people with FH.

3.3. Trials

In the excitement over the successful statin trials, many researchers seem to have forgotten that meta-analyses of all controlled, randomized cholesterol lowering nonstatin trials found no effect on CHD or total mortality' neither was the outcome associated with the degree of cholesterol lowering [1,54]. Although the statin trials have been successful, the effect on CHD reduction was achieved independently of the initial cholesterol level, or on the degree of cholesterol lowering, for example, there was lack of exposure– or dose–response [55], strongly suggesting that the effect of the statins has nothing to do with their ability to lower cholesterol levels [56].

In addition, exposure–response was absent in almost all angiographic studies, because sequential changes of atherosclerosis did not correlate with sequential changes of cholesterol [1,57–59].

3.4. Why does high cholesterol predict CHD?

Each of the many contradictory observations mentioned above effectively falsifies the idea that high cholesterol is the main cause of atherosclerosis. The reason why high cholesterol has been found to be predictive of CHD in many studies may be that the true causes of CHD may also raise cholesterol. Several factors can do this; most important are, probably, mental stress [60], physical inactivity [61], and smoking [62]. It is a general belief that the cardiovascular risk associated with these factors is mediated through their effects on LDL- and high-density lipoprotein (HDL)-cholesterol. However, their effect on CHD may be more direct. Mental stress affects adrenal function, smoking may increase the burden of oxidants and

thus directly damage the endothelium, and physical inactivity may prevent the formation of collateral vessels in the coronary arterial system [63] and/or compromise coronary endothelial function [64].

4. The response to crisis

So how is it that the diet heart idea is still alive despite the enormous amount of contradictory evidence? There are many explanations.

Many authors construct ad hoc modifications of the diet–heart idea to explain their findings. As the number of "risk factors" for CHD now stretches to many hundreds, it is always possible to explain away contradictory results by referring to an imbalance of other risk factors, known or unknown. According to Karl Popper, the hallmark of a scientific hypothesis is that it is falsifiable. Yet, all facts that contradict the diet–heart hypothesis are explained away by the creation of more and more ad hoc hypotheses, for instance, by claiming protective effects from red wine and MUFA consumption, low SFA/PUFA ratios, a Mediterranean diet, etc. This has, effectively, resulted in a nonfalsifiable hypothesis, meaning that it may be more accurate to classify the diet–heart hypothesis as nonscience.

An impression of general agreement is created by citing supportive or allegedly supportive studies only [65]. In a meta-analysis of the cholesterol-lowering trials I found that in the trial reports a total of 40 supportive or inconclusive trials were cited, but, with one exception, not a single unsupportive one. This is despite the fact that the total number of supportive and unsupportive trials were actually equal. I also found that, according to Science Citation Index, the mean overall annual citation of the supportive trials was 40, whereas the unsupportive trials were cited on average 7.4 times per year. For example, the allegedly supportive Lipid Research Clinics trial was cited 612 times during the first 4 years after its publication, yet the nonsupportive trial by Miettinen et al. [54] was cited only 15 times. Interestingly, both of these trials were published in the same medical journal.

Very often the authors' own contradictory findings are not mentioned in the discussion, or in the summary of their article. Equally, nonsignificant findings are mentioned in the abstract as if they were positive. The first variant appeared in six of the studies mentioned in Table 1 [28,29,31–33,37]; the other was seen in four of the studies [28,29,34,38].

Also, authors of authoritative reviews misquote. In an analysis of the quotations from three such reviews [66–68] I found that only 2 of 12 selected groups of contradictory studies were quoted correctly, and only in one of the reviews. About half of the contradictory papers were ignored; the rest were quoted irrelevantly; or insignificant findings in favour of the hypothesis were inflated; or unsupportive results were quoted as if they were supportive [65].

In a recent and thorough analysis of the history and the political background of the diet–heart hypothesis, published recently in Science Magazine, Gary Taubes concluded that, despite 50 years of research, we still have no evidence that a low-fat diet will prolong life [69]. In a letter to the editor, Scott Grundy, a prominent supporter of the diet–heart hypothesis, answered Taubes by claiming that SFA are the main dietary cause of coronary heart disease [70] referring to a number of studies, that either had not dealt with that issue, or were contradictory [71].

5. Conclusions

A large number of scientific studies contradict the hypothesis that dietary fat and high cholesterol play a major role in the causation of atherosclerosis and cardiovascular disease. Readers may probably object that I have preferably picked contradictory studies out of a huge number of supportive ones. However, a thorough examination of the literature in this area [1] has convinced me that most studies are either useless for determining causality, or they are contradictory. But even if many studies were supportive, a valid hypothesis should withstand all attempts of falsification. One single study that falsifies it and which is based on verifiable observations should suffice for its rejection.

There are many, more or less probable, alternative hypotheses about the causation of atherosclerosis and cardiovascular disease, but the maintenance of the diet–heart hypothesis by prestigious and powerful scientists and organizations retard their exploration by turning away intellectual and financial resources. Worse is the fact, that any new discovery is twisted and bent to tally with the current concept, not to mention the negative effects on public health, food production, and the health and general well-being of millions of people. It would be a great contribution to science and mankind if influential institutions could break the vicious cycle by supporting researchers who create hypotheses that fit their data, instead of researchers who interpret their data to fit a predetermined hypothesis.

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