The Diet-Heart Hypothesis: Changing Perspectives

Dr Amitav Banerjee

Address for correspondence: Dr Amitav Banerjee, Professor and Head, Department of Community Medicine, Dr D Y Patil Medical College, Hospital and Research Centre, Dr DY Patil Vidyapeeth, Pune – 411018, India

Email: amitavb@gmail.com

ABSTRACT

The diet-heart hypothesis, i.e. dietary cholesterol and saturated fats raise the serum cholesterol which in turn is a risk factor for coronary artery disease is prevalent since the 1950s. Over the years it had a major influence on the perspectives of nutritionists, medical researchers and the lay public. However, of late, the evidence base supporting the diet-heart hypothesis is being increasingly questioned. Besides retrieval and re-analysis of archival data from incomplete studies, study of internal documents of industry reveal that vested interests may have played a role in maintaining the diet-heart hypothesis. This brief review gives an overview of the evidence and conflicting views most of which fell by the wayside in the heady days of the diet-heart hypothesis. It puts forth the question whether there is a paradigm shift in the diet-heart hypothesis. Using the key-words "diet-heart hypothesis" an online literature search was made using PubMed, Scopus and Google Scholar. Standard texts on nutritional epidemiology and other writings on the subject were reviewed.

Keywords: Diet-heart hypothesis; evidence base; paradigm shift; coronary heart disease

INTRODUCTION

The Nobel Prize winning scholar Kahneman has coined the phrase “thinking fast and slow.”[1] Thinking fast is intuitive while thinking slow is more deliberate. While intuitive thinking is fast and saves time, on occasions it can be biased. In some situations deliberate and slow thinking provides answers nearer to the truth. The diet-heart hypothesis first proposed by Ancel Keys is based on the presumption that dietary cholesterol and saturated fats raise serum cholesterol which in turn is a risk factor for coronary artery disease.[2] Based on this hypothesis, dietary guidelines in many countries were laid down over the years. These recommended promotion of low fat diets, and restricting dietary cholesterol.

Food items such as whole fat milk, whole eggs, and red meat were thought to increase risk of coronary heart disease. Even to this day; this is the consensus among nutrition scientists, medical researchers, practitioners and the lay public. This line of thinking seems intuitively right too. That dietary fat and cholesterol will raise serum cholesterol appears plausible. Serum cholesterol depositing in the coronaries causing atherosclerosis appears intuitively correct. This is thinking fast.

However, over the years, slow thinkers have identified fault-lines in the diet-heart hypothesis and they seem to be catching up with the fast thinkers. This overview firstly, traces the evolution of the diet-heart hypothesis and secondly, weighs the overlooked and accumulating evidence challenging it.

An online literature search was carried out using the keywords "Diet-Heart Hypothesis" through PubMed, Scopus and Google Scholar. Besides, standard texts on nutritional epidemiology and other relevant texts were also consulted. Papers were purposefully selected to narrate the evolution of the diet heart hypothesis and identify dissenting views which fell by the wayside. Some recent papers which vindicate the alternative views ignored by the scientific community of yesteryears were also selected.

Genesis of the Diet-Heart Hypothesis - effect of dietary cholesterol - from laboratory to practice.

In the early twentieth century the Russian pathologist Anitschkow induced atherosclerosis in rabbits by putting them on cholesterol rich diet.[3] This finding replicated in other herbivorous animals led to the widespread belief that cholesterol in the diet can lead to atherosclerosis. Some investigators did recommend caution in generalizing this observation from the laboratory as they pointed out that experiments were done in herbivorous animals. When researchers tried to replicate this experiment in dogs which are carnivorous they found excess cholesterol was excreted thus regulating the serum cholesterol level.[4,5] The experiment in the dog offered a better model for human cholesterol metabolism. However, the earlier rabbit experiments had a greater impact on the scientific community and established cholesterol as the main risk factor for coronary heart disease. The medical consensus evolved that it would be prudent to maintain serum cholesterol at low levels. The proposition that dietary cholesterol would cause higher levels of serum cholesterol was put forth.[6] Over the years this view became widespread. Even today we see "zero cholesterol" labels on food items in the supermarket.

That Keys, the father of the diet-heart hypothesis himself refuted this proposition is overlooked. Though on one hand Keys stated that there is overwhelming evidence that dietary cholesterol raises serum cholesterol,[7] he could not induce appreciable rise in serum cholesterol by feeding very large doses up to 3000 mg of dietary cholesterol to human participants.[8] Keys suggested that since dietary cholesterol has no effect on serum cholesterol one should focus on other aspects of the diet. As a result lipid research became priority.

Research on different types of fats and serum cholesterol.

Researchers in early 1950s noted that replacing animal fat with vegetable fat reduces serum cholesterol.[9] Serum cholesterol was also reported to be lower in vegetarians.[10, 11] Ahrens and colleagues carried out a number of studies to establish association of different types of fats with serum cholesterol.[12, 13, 14, 15] It was observed that saturated fat in butter and coconut oil raised serum cholesterol more than any other fats, while the lowest serum cholesterol was associated with peanut, cottonseed, corn and safflower oils. An important aspect noted was that there was much variance in the response to dietary fats. There was no consistency in the relation between fats in the diet and serum cholesterol. This "heterogeneity" of individual responses according to Ahren's statement was the most "gratifying contribution" to lipid research. Ignoring this need for restraint in generalizing the results from few subjects, investigators have tended to believe that these cholesterol responses were uniform which focused the attention on saturated fats as the culprit in raising serum cholesterol and risk of coronary artery disease.[16]

Keys conducted number of trials on 66 male schizophrenic patients (no ethical committee would approve this trial today).[17] They were put on diets containing fat content ranging from 9% to 24%. Lower range of dietary fat was associated with lower levels of serum cholesterol. Besides the ethical issues, the study had number of limitations including a small non-representative sample which were glossed over.[16] In spite of this, Keys promoted the findings to suggest that there is little room for doubt.

Ecological studies

In the early 1950s, Keys presented ecological data from six countries to support his diet-heart hypothesis. His graph showed a close correlation between consumption of fat and deaths from heart disease in these countries.[18] However, others suspected cherry picking of the data. Yerushalmy, a biostatistician was one of them. He stated that Keys only selected the six countries because the data from them conformed to his hypothesis. The trend noted by Keys in these six countries could be due to ecological fallacy, i.e., presence of other confounding factors such as increasing trends of cars, tobacco consumption, sedentary lifestyle and sugar consumption. When Yerushalmy along with his colleague, extended this ecological analysis to twenty two countries instead of the six which Keys had selected, the correlation between population level fat consumption and heart disease almost disappeared.[19]

Keys' ecological study was also criticized by Mann who found no rise in serum cholesterol or coronary heart disease in Masai tribe in Kenya, in spite of very high consumption of saturated fats.[20, 21] Mann even predicted the end of the "diet-heart era."[22]

The seven countries study

One of the most cited studies supporting the diet-heart hypothesis is the "Seven Countries Study," which was launched by Ancel Keys in 1956.[23] In this study more than 12, 500 middle aged men in seven countries – Italy, Greece, Yugoslavia, Finland, Netherlands, Japan and the United States were followed up. Critics have since challenged the selection of the countries.[24, 25] They contend that had Keys seriously wanted to maintain an objective approach, he should have chosen countries like Switzerland, France, Germany, Norway and Sweden. Instead, he selected a purposive sample of countries which could have led to selection bias. Besides this bias there were other factors in the time period of the study which could have confounded the association between dietary fat and coronary heart disease. One was the slow recovery of the economy in the Mediterranean countries post World War II leading to an austere lifestyle.[16]

In this study, researchers visited populations and measured serum cholesterol, weight, blood pressure and noted the dietary and smoking histories. The seven countries study found a strong correlation between dietary saturated fat and heart disease. [23] This is one of the most cited studies by the proponents of the diet-heart hypothesis. However, some unanswered questions exist in the study. The rate of coronary events in Eastern Finland was three times more than Western Finland in spite of identical diet and lifestyles. Similarly inhabitants of Corfu islands consumed less saturated fats than their countrymen in Crete yet the rate of coronary heart disease was higher in Corfu.[16]

Detailed scrutiny of the methodology of the seven countries study reveals some glaring measurement errors.[26] In the surveys in Greece (where the concept of Mediterranean diet originated), Keys and his co-workers had sampled diets in Crete and Corfu number of times to capture the variation in food consumption. One major oversight made by these workers was that one of the major surveys undertaken was during the 48 days fasting period of Lent - the Greek orthodox fast is very strict where meat, eggs, cheese or any other food of animal origin is forbidden. Since these foods are the principal source of saturated fat, surveys during this period will grossly underestimate the saturated fat intake of the population. A study conducted in Crete reported saturated fat consumption halved during Lent.[27]

Does restriction of saturated fats increase longevity?

The follow up of the seven countries study threw up more contentious issues. In 1984, Keys and his co-investigators resurveyed these populations.[28, 29] Over the years the association of dietary saturated fat and heart disease had become much weaker. Another interesting finding was that though consumption of saturated fat was associated with higher deaths from heart disease, it was associated with lesser overall mortality. Longevity was not related to saturated fat or cholesterol in the diet or to the level of serum cholesterol.

Follow up of a study launched in 1957 reported similar outcomes. [30, 31, 32] Eleven hundred men were enrolled in a study to see the effects of dietary modification on coronary heart disease and longevity. They were advised to reduce their consumption of red meat, and told to increase consumption of poultry and fish. Eggs and dairy products were restricted. In addition, they took two tablespoons of vegetable oil daily. Overall the ratio of polyunsaturated fats to saturated fats was four times the normal American diet while calorie from fat in the diet was 30%. A control group was also enrolled who consumed the normal American diet of the day with 40% calories from fats (mostly saturated). [30]

The study found that in the initial five years of the trial, serum cholesterol, blood pressure and body weight dropped in the intervention group. However, over a decade of follow up, the mortality was higher in the intervention group.[32] This contradictory result has been glossed over.[16]

Another study among 850 veterans showed that while replacement of saturated fats with polyunsaturated fats brought down the mortality from coronary heart disease it had no impact on overall longevity. [33] More alarmingly, thirty one veterans on polyunsaturated fat group died of cancer compared to seventeen in the control group.[34] Such unexpected findings seem to have been sidetracked in the fast track push for the diet-heart hypothesis.

Framingham Heart Study and its lesser known facts

Since 1948, Framingham Heart Study has been the "petri dish" for the study of risk factors for coronary heart disease.[16] The study began with about 5000 middle aged participants of both gender in Boston, USA. It was a classical cohort study to identify whether factors such as diet, cigarette smoking, family history, and hypertension could predict incidence of coronary heart disease. Participants were followed up every two years. In 1961, the study found that high serum cholesterol was a risk factor for coronary heart disease. [35] This finding was the foundation for serum cholesterol getting elevated as a "surrogate" marker for prediction of coronary heart disease morbidity. The diet-heart hypothesis seemed to rest on strong foundation.

What is lesser known is further follow up results. Thirty years later with more data and mortality outcomes, the predictive power of serum cholesterol was not found to be so strong as the earlier results.[36] Paradoxically, lower serum cholesterol was associated with higher overall mortality – for each 1% mg/dL fall in cholesterol there was an 11% rise in coronary and overall mortality.[36] The authors concluded that below 50 years, lower serum cholesterol may be protective to coronary mortality and morbidity while after this age, the association may be confounded because of co-morbidities.[36] Mann and his colleagues also did not find any correlation between dietary saturated fat and heart disease on analysis of Framingham follow up data.[37]

Indian study refuting the diet-heart hypothesis

An Indian study did find an association of dietary factors with coronary heart disease but in a direction which challenges the diet-heart hypothesis.[38, 39, 40] Among more than a million railway employees in India, the five year rate of coronary heart disease was seven times higher in workers from southern India, compared to those from the Punjab.[39] Paradoxically, from the point of view of the diet-heart hypothesis, the north Indians were consuming eight to nineteen times more saturated fats compared to the south Indians. The southerners also died on an average twelve years earlier than their north Indian counterparts. The author recommended a diet containing more milk products, yogurt, and butter.[40] The findings of this study though published in international journals did not attract the attention of the world scientific community nor did receive enough citations.

Early case control studies challenging the diet heart hypothesis

Zukel et al[41] identified 228 cases who had a myocardial event or mortality, and retrospectively compared the risk factors of 162 cases with controls. Beyond heavy smoking no other association with any risk factors such as calorie consumption or dietary fat in the diet could be established in this study. Similarly, in Ireland, diets of 100 men with myocardial infarction were compared with age and gender matched controls.[42] No association of coronary event was found with amount of dietary fat. The same investigators repeated the study in 50 women who suffered a myocardial event.[43] In this study also there was no "diet heart association."The authors concluded that though Ancel Keys had proposed the "diet heart hypothesis" (at that time based on ecological studies),[18] their case control studies at individual levels failed to support this hypothesis.

LDL-cholesterol, HDL-cholesterol and triglycerides.

Total serum cholesterol is composed of low density lipoproteins (LDL) and high density lipoprotein (HDL). While LDL-cholesterol is a risk marker for coronary heart disease, HDL-cholesterol is protective.[44, 45] It was gradually realised that

rather than total serum cholesterol, complex mix of other factors in the blood such as LDL-cholesterol, HDL- cholesterol and triglycerides were important predictors of risk from coronary heart disease. There are concerns that while restriction of dietary saturated fats may lower total and LDL cholesterol it will also lower HDL-cholesterol. This may offset any advantage one may expect by lowering total and LDL-cholesterol.

While high levels of the good cholesterol HDL is equally important, most attention and research is devoted to lowering total and LDL cholesterol.[16] There are concerns that this is driven by market forces promoting cholesterol lowering "statin" drugs.[16, 46] There is also a view that while statins may lower the risk of coronary event their action may not be solely by lowering serum cholesterol but by their anti-inflammatory action.[47]

With the focus on dietary fats and serum cholesterol in the early years of the diet-heart hypothesis few scientists studied serum triglycerides as a risk factor. Among those raising concern were Ahrens[48] and Albrink.[49] Ahrens work indicated that carbohydrates found in cereals and sugar might be contributing to obesity and disease. He also demonstrated that substituting fats in the diet with carbohydrates raised the serum triglycerides level.[50] Albrink also demonstrated that in patients of coronary heart disease, serum triglycerides were more likely to be elevated than serum cholesterol.[51] However, Ahrens and Albrink's studies done in the 1950s and 1960s were far ahead of their time and this path of investigation did not have many followers. Only recently has the association between carbohydrate intake and coronary heart disease and other chronic diseases have attracted the attention of researchers.[52, 53]

Trans fats

As the diet-heart hypothesis gained popularity, the search for alternative cooking medium to saturated fats led to increasing use of hydrogenated vegetable oils. By the late 1980s these oils were used extensively in the food industry. Partial hydrogenation of vegetable oils create trans fats, which are being increasingly recognized as a risk factor for many chronic diseases including coronary artery disease, insulin resistance and obesity.[54]

Trans fats also occur in nature. These naturally occurring trans fats are present in the meat and milk of ruminant animals and are called, "ruminant trans fats." Ruminant trans fats resemble those found in partially hydrogenated vegetable oils and share the common formula. However they have a double bond on a different position – this subtle difference is believed to render them less harmful.[55, 56, 57, 58]

Recent papers challenging the diet heart hypothesis

Till now we have reviewed some dissenting voices to the diet-heart hypothesis in its formative years and evolution. Due to the stature and influence of its founder Ancel Keys these voices were muffled and scientists who questioned the hypothesis suffered reverses in their career and did not get research grants.[16] In the subsequent paragraphs we will review some recent papers challenging the diet-heart hypothesis.

Recovery and analysis of archival data

Ramsden et al, appraised the evidence supporting the diet-heart hypothesis by recovering and analysing archival unpublished data from the Sydney Diet Study (SDHS, 1966 – 73) and the Minnesota Coronary Experiment in context of existing randomized controlled trials (RCTs) by doing a systematic review and meta-analysis.[59, 60]

The SDHS was a randomized controlled dietary trial to study the effects of replacing saturated fats in the diet with linoleic acid (LA) in safflower oil in the secondary prevention of coronary heart disease.[61,- 66] The limitation of this study was that though increase in all cause mortality was reported in the safflower oil group,[61] group wise deaths from cardiovascular and coronary heart disease were not reported. These are more relevant when appraising the evidence base for the diet-heart hypothesis.

Ramsden et al, recovered SDHS data set and used present day statistical methods to reanalyse and compare rates from all causes including coronary cardiovascular and coronary heart disease mortality and update a similar meta-analysis undertaken a few years ago.[67] The reanalysis showed that the intervention group receiving safflower oil (221 participants), had higher rates of deaths at 17.6% than the controls (237 participants), in which the rate was 11.8%. From this updated meta-analysis the authors concluded that though worldwide the guidelines for prevention of coronary heart disease include advice on replacing saturated fats in the diet with polyunsaturated fats, the clinical benefits of this practice has not been established. In their analysis the intervention group in which dietary linoleic acid in form of safflower oil was given in place of dietary saturated fats had higher all cause mortality as well as increased mortality from cardiovascular and coronary heart disease. The authors express that the findings have implications for reconsidering the practice of advising replacement of dietary saturated fats with polyunsaturated fats.[59]

Similarly, recovered data from the Minnesota Coronary Experiment (1968 – 73), was also re-evaluated by Ramsden et al.[60] This was a double blind randomized controlled trial to see whether replacement of saturated fats with vegetable oils rich in linoleic acid reduces serum cholesterol and brings down the mortality from coronary events. This was the largest dietary

trial with 9570 participants.[60] The trial also included autopsy for evidence of atherosclerosis. The results of re-evaluation of the trial data showed that though the intervention group had reduction in serum cholesterol this was not translated into reduced mortality. Moreover, there was no evidence of benefit of dietary polyunsaturated fats for atherosclerosis or myocardial infarcts. Systemic review and meta-analysis of five randomized controlled trials (10808 participants), did not reveal any reduction of mortality from coronary heart disease or overall mortality.[60]

Willett and Stampfer[68] concede that though abundant evidence may suggest that dietary fatty acids play role in coronary artery disease, the dose-response relationships between specific fatty acids and cholesterol intake and rates of coronary heart disease are not clearly defined. There may be modest impact which may be lost if saturated fats is replaced by carbohydrate in the diet.

Reinventing the buried wheels

A number of recent studies have generated views similar to some in the early days of the diet-heart hypothesis. However these views lacked the "stickiness-factor" required to hold the attention of the scientific community. During its evolution, the wave of the diet-heart hypothesis was strong enough to wash away all opposition. These dissenting views were the buried wheels which had to be reinvented.

For instance Ahrens and his colleagues carried out a number of studies in the 1950s to study the effect of dietary fat on serum cholesterol.[12, 13, 14, 15] One of his important inferences from these studies was that there was much "heterogeneity" in individual responses leading to much variance in serum cholesterol levels in response to dietary fat – "one size did not fit all." Because of such variation it would was not prudent to make dietary guidelines based on the diet-heart hypothesis. A recent systematic review echoes these views.[69] The authors of this review state that current evidence is limited but suggestive of much genetic variation in the lipid response to dietary intervention. Insights into gene-diet interactions will increase our understanding of pathways of lipid metabolism and role of diet in modifying cardiovascular risk.[69]

Decades ago, Albrink[49, 51] and Ahrens[48, 50] had expressed concerns about replacing dietary fats with dietary sugars causing increase in serum triglycerides associated with increased risk of coronary heart disease. Had this line of research received more attention earlier we might have prevented a large number of morbidity from cardiovascular and other chronic diseases. Besides the fast track mode of promotion of the diet-heart hypothesis in those days, there were other factors at play including market forces. Recent scrutiny of sugar industry documents in USA suggest that sugar industry sponsored research in the 1960s and 1970s undermined the hazards of sugar while promoting dietary saturated fat as the major risk factor.[70]

Recently, DiNicolantonio et al[71] reviewed the evidence for saturated fat and for sugar related to coronary heart disease. They concluded that while dietary guidelines even today advise restriction of saturated fat to check serum cholesterol which is only modestly associated with cardiovascular mortality; sugars and refined carbohydrates carry a greater risk. They caution that when dietary saturated fats are replaced by sugars and refined carbohydrates the risk of coronary heart disease may increase threefold.[71]

CONCLUSION

Epidemiological studies which were helpful in communicable diseases have their limitations when applied to chronic diseases.[16] Chronic diseases have a long latent period and have multiple causative and confounding factors. Nutritional epidemiology is limited by number of biases and measurement errors. It is not feasible to administer a diet plan on a population and keep all variables constant over a number of years. It is also difficulty to keep participants restricted to a rigid lifestyle.

This "quick and dirty" nature of nutritional studies and "thinking fast" mode promoted by different stakeholders, led to the simplistic "diet-heart" hypothesis in spite of intersperse of "slow thinkers" who were condemned to obscurity. Only recently the "slow thinkers" seem to be catching on and reanalysis of important archival data may unravel the nuances of diet and disease. Increasingly it is being realized that dietary carbohydrates and increased serum triglycerides pose stronger risk than dietary fats for cardiovascular and other chronic diseases. This is of relevance to the Indian population as our carbohydrate consumption is on the higher side. We need more indigenous studies of good quality urgently as our burden of chronic diseases is increasing.

Though recent accumulating evidence may bring about a paradigm shift in the diet-heart hypothesis, this may not be abrupt. Conflicts of interest among market forces and other stakeholders may tend to maintain the status quo.[72]

REFERENCES

1. Kahneman D. Thinking fast and slow. London. Penguin Random House UK. 2011
2. Keys A. Atherosclerosis: A problem in newer public health. J Mt Sinai Hosp NY 1953; 20:118 – 39.
3. Konstantinov IE, Mejevoi N, Anichkov NM. Nikolai N. Anichkov and His Theory of Atherosclerosis. Texas Heart Institute Journal. 2006;33(4):417-423.

4. Gould R G. Lipid metabolism and atherosclerosis. Journal of Medicine 1951; 11: 2: 209 - 227.

5. Gould R G, Taylor C B, Hagerman J S, Warner I, Campbell D J. Cholesterol metabolism: 1. Effect of Dietary Cholesterol on the Synthesis of Cholesterol in Dog Tissue in Vitro. Journal of Biological Chemistry 1953; 201: 2: 519 – 528.

6. Rittenberg D, Schoenheimer R. Deuterium as an indicator in the study of intermediary metabolism XI. Further studies on the biological uptake of deuterium into organic substances with special references to fat and cholesterol formation. Journal of Biological Chemistry 1937; 121: 1: 235 - 253.

7. Keys A. Human atherosclerosis and the diet. Circulation 1952; 5: 115 - 118.

8. Keys A, Anderson J T, Fidanza F, Keys M H, Swahn B. Effects of diet on blood lipids in man particularly cholesterol and lipoproteins. Clinical Chemistry 1955; 1: 1: 40 - 52.

9. Kinsell L S, Partridge J, Boling L, Margen S, Michaels G, Olson F, et al. Dietary modifications and serum cholesterol and phospholipid levels. Journal of Clinical Endocrinology and Metabolism 1952; 12: 7: 909 - 913.

10. Hardinge M G, Stare F J. Nutritional Studies of Vegetarians: 2. Dietary and serum levels of cholesterol. Journal of Clinical Nutrition 1954; 2: 2: 82 - 88.

11. Groen J, Tjiong B K, Kamminga C E, Willebrands A F. Influence of nutrition, individual and some other factors, including various forms of stress on serum cholesterol; experiment of nine months duration in 60 normal human volunteers. Voeding 1952; 13: 556 - 587.

12. Ahrens E H Jr, Blankenhorn D H, Tsaltas, T T. Effect on Human Serum Lipids of substituting Plant for Animal Fat in Diet. Proceedings for the Society of Experimental Biology and Medicine 1954; 86: 4: 872 – 878.

13. Ahrens E H Jr, Hirsch J, Insull W Jr, Tsaltas T T, Blomstrand R, Peterson M. Dietary control of serum lipids in relation to atherosclerosis. Journal of the American Medical Association. 1957; 164: 17: 1905 – 1911.

14. Ahrens E H Jr, Hirsch J, Oette K, Farquhar J W, Stein Y. Carbohydrate induced and fat induced lipemia. Transactions of the Association of American Physicians 1961; 74: 134 – 146.

15. Ahrens E H Jr, Insull W Jr, Blomstrand R, Hirsch J, Tsaltas T T, Peterson M L. The influence of dietary fats on serum lipid levels in Man. Lancet 1957; 272: 6976: 943 – 953.

16. Teicholz N. The big fat surprise. New York. Simon & Schuster. 2014.

17. Keys A, Anderson J T, Grande F. Prediction of serum-cholesterol response of man to changes in fats in the diet. Lancet 1957; 273: 7003: 959 – 966.

18. Keys A. Atherosclerosis: A problem in newer Public Health. Journal of Mt Sinai Hospital New York 1953; 20: 2: 118 – 139.

19. Yerushalmy J, Hilleboe H E. Fat in the diet and mortality from heart disease: A methodologic note. New York State Journal of Medicine 1957; 57: 14: 2343 – 2354.

20. Mann G V. Diet and coronary heart disease. Archives of Internal Medicine 1959; 104: 921 – 929.

21. Mann G V, Shaffer R D, Anderson R S, et al. Cardiovascular disease in the Masai. Journal of Atherosclerosis Research 1964; 4: 4: 289 – 312.

22. Mann G V. Diet-Heart: End of an Era. New England Journal of Medicine 1977; 297: 12: 644 – 650.

23. Keys A, ed. Coronary Heart Disease in Seven Countries. Circulation 1970; 41 & 42: 1: Supplement 1: American Heart Association Monograph No 29: 1 – 211.

24. Ravenskov U. The cholesterol myths: exposing the fallacy that saturated fat and cholesterol cause heart disease. Washington D C: New Trends, 2000.

25. Taubes G. Good calories, bad calories: fats, carbs, and the controversial science of diet and health. New York: Alfred A. Knopf, 2007.

26. Sarri K, Kafatos A. The seven countries study in Crete: Olive oil, Mediterranean Diet or Fasting? Public Health Nutrition 2005; 8: 6: 666.

27. Sarri K, Linardakis M K, Bervanaki F N, Tzanakis N E, Kafatos A G. Greek orthodox fasting rituals: A hidden characteristic of the Mediterranean diet of Crete. British Journal of Nutrition 2004; 92: 2: 277 - 284.

28. Keys A, Menotti A, Aravanis C, et al. The seven countries study: 2,289 deaths in 15 years. Preventive Medicine 1984; 13: 2: 141 – 154.

29. Keys A, Menotti A, Karvonen M J, et al. The diet and 15 year death rate in the seven countries study. American Journal of Epidemiology 1986; 124: 6: 903 – 915.

30. Jolliffe N, Rinzler S H, Archer M. The anti-coronary club: including a discussion on the effects of a prudent diet on the serum cholesterol level of middle aged men. American Journal of Clinical Nutrition 1959; 7: 4: 451 – 462.

31. Christakis G, Summary of the research activities of the anti-coronary club. Public Health Reports 1966; 81: 1: 64 – 70.

32. Christakis G,Rinzler S H, Archer M. Effect of the anti-coronary club program on coronary heart disease risk factor status. Journal of the American Medical Association 1966; 198: 6: 597 – 604.

33. Dayton S, Pearce M L, Hashimoto S, Dixon W J, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation 1969; 40: 1: suppl 2: II – I

34. Pearce M L, Dayton S. Incidence of cancer in men on a diet high in polyunsaturated fat. Lancet 1971; 297: 7697: 464 – 467.

35. Kannel W B, Dawber T R, Kagan A, Revotskie N, Stokes J. Factors of risk in development of coronary heart disease – six years follow up experience. The Framingham Study. Annals of Internal Medicine 1961; 55: 1: 33 – 50.

36. Anderson K M, Castelli W P, Levy D. Cholesterol and mortality: 30 years of follow up from the Framingham study. Journal of the American Medical Association. 1987; 257: 16: 2176 – 2180.

37. Mann G V, Pearson G, Gordon T, Dawber T R, Lyell L, Shurtleff D. Diet and Cardiovascular disease in the Framingham study I. Measurement of dietary intake. American Journal of Clinical Nutrition 1962; 11: 3: 200 – 225.

38. Malhotra S L. Geographical aspects of acute myocardial infarction in India with special reference to patterns of diet and eating. British Heart Journal 1967; 29: 3: 337 – 344.

39. Malhotra S L. Epidemiology of Ischemic heart disease in Southern India with special reference to causation. British Heart Journal 1967; 29: 6: 895 – 905.

40. Malhotra S L. Dietary factors and Ischemic heart disease. American Journal of Clinical Nutrition 1971; 24: 10: 1195 – 1198.

41. Zukel W J, Lewis R H, Enterline P E. A short term community study of coronary heart disease: A preliminary report on the North Dakota study. American Journal of Public Health and the Nation's Health 1959; 49: 12: 1630 - 1639.

42. Finnegan A, Hickey N, Maurer B, Mulcahy R. Diet and coronary heart disease: Dietary analysis on 100 male patients. American Journal of Clinical Nutrition 1968; 21: 2: 143 - 148.

43. Finnegan A, Hickey N, Maurer B, Mulcahy R. Diet and coronary heart disease: Dietary analysis on 50 female patients. American Journal of Clinical Nutrition 1969; 22: 1: 8 - 9.

44. Gordon T, Castelli W P, Hjortland M C, Kannel W B, Dawber T R. High density lipoprotein as a protective factor against coronary heart disease: The Framingham study. American Journal of Medicine 1977; 62: 5: 707 – 714.

45. Castelli W P, Doyle J T, Gordon T, et al. HDL cholesterol and other lipids in coronary heart disease: the cooperative lipoprotein phenotyping study. Circulation 1977; 55: 5: 767 – 772.

46. Fuhrmann R. 5-best-selling-prescription meds of all time. Investopedia. September 24, 2012. Accessible at: https://www.investopedia.com/financial-edge/0912/5-best-selling-prescription-meds-of-all-time.aspx (accessed 24/11/2017)

47. LaRosa J C. Grundy S M, Waters D D, Shear C, Barter P, Fruchart J C, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. New England Journal of Medicine 2005; 352: 14: 1425 – 1435.

48. Ahrens E H Jr. Carbohydrates, plasma triglycerides and coronary heart disease. Nutrition reviews 1986; 44: 2: 60 – 64.

49. Albrink M J. Triglycerides, lipoproteins, and coronary heart disease. Archives of Internal Medicine 1962; 109: 3: 345 – 359.

50. Ahrens E H Jr, Blankenhorn D H, Tsaltas T T. Effect on human serum lipids of substituting plant for animal fat in diet. Proceedings for the Society of Experimental Biology and Medicine 1954; 86: 4: 872 – 878.

51. Albrink M J. The significance of serum triglycerides. Journal of the American Dietetic Association 1963; 42: 29 – 31.

52. Mozaffarian D. Effects of dietary fats versus carbohydrates on coronary heart disease: a review of the evidence. Current Atheroscler 2005; 7: 6: 435 – 45

53. Kuipers R S, de Graff D J, Luxwolda M F, Muskiet M H, Dijck-Brouwer D A, Muskiet F A. Saturated fat, carbohydrate and cardiovascular disease. Neth J Med 2011; 69: 9: 372 – 8.

54. Mozaffarian D, Aro A, Willett W C. Health Effects of trans-fatty acids: experimental and observations evidence. Eur J ClinNutr 2009; 63: Suppl 2: S5 - 21. doi: 10.1038/sj.ejcn.1602973.

55. Kummerow F A, Zhou S Q, Mahfouz M M. Effects of trans fatty acids on calcium influx into human arterial endothelial cells. American Journal of Clinical Nutrition 1999; 70: 5: 832 – 838.

56. Lawson L D, Kummerow F A. B-oxidation of the coenzyme A esters of vacenic, elaidic and petroselaidic acids by rat heart mitochondria. Lipids 1979; 14: 5: 501 – 503.

57. Bendsen N T, Christensen R, Bartels E M, Astrup A. Consumption of Industrial and Ruminant trans fatty acids and risk of coronary heart disease. A systemic review and meta-analysis of cohort studies. European Journal of Clinical Nutrition 2011; 65: 7: 773 – 783.

58. Ganguly R, Pierce G N. The toxicity of dietary trans fats. Food ChemToxicol 2015; 78: 170 – 6. doi: 10.1016/j.fct.2015.02.004. Epub 2015 Feb 12.

59. Ramsden C E, Zamora D, Leelarthaepin B, Majchrzak-Hong S, Faurot K R, Suchindran C M et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ 2013; 346:e8707.doi:10.1136/bmj.e8707.

60. Ramsden C E, Zamora D, Majchrzak-Hong S, Faurot K R, Broste S K, Frantz R P, et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968 – 73). BMJ 2016 Apr 12;353:i1246. doi: 10.1136/bmj.i1246.

61. Woodhill JM, Palmer AJ, Leelarthaepin B, McGilchrist C, Blacket RB. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. Adv Exp Med Biol1978;109:317-30.

62. Palmer J, Leelarthaepin B, McGilchrist C, Blacket R. Coronary heart disease profile in Australian men and some factors influencing survival. Adv Exp Med Biol1977;82:115-7.

63. McGilchrist CA, Leelarthaepin B, Blacket RB. Measures on qualitative variables in coronary heart disease studies. J Chronic Dis1976;29:285-8.

64. Blacket RB, Leelarthaepin B, Palmer AJ, Woodhill JM. Coronary heart disease in young men: a study of seventy patients with a critical review of etiological factors. Aust N Z J Med 1973;3:39-62.

65. Blacket RB, Leelarthaepin B. Coronary disease in young men. Singapore Med J 1973;14:344-6.

66. Blacket RB. Diet in prevention of heart disease. Med J Australia1973;1:969-73.

67. Ramsden CE, Hibbeln JR, Majchrzak SF, Davis JM. n-6 fatty acid-specific and mixed polyunsaturate dietary interventions have different effects on CHD risk: a meta-analysis of randomised controlled trials. Br J Nutr 2010;104:1586-600.

68. Willett W C, Stampfer M. Diet and Coronary Heart Disease. In: Nutritional Epidemiology. Third edition. Willett W [ed]. Oxford. Oxford University Press. 2013; 426 – 467.

69. Masson L F, McNeill G, Avenell A. Genetic variation and the lipid response to dietary intervention: a systemic review 1'2'3. The American Journal of Clinical Nutrition 2003; 77: 5: 1098 – 1111.

70. Kearns C E, Schmidt L A, Glantz S A. Sugar Industry and Coronary Heart Disease Research: A historical analysis of Internal Industry Documents. JAMA Intern Med 2016; 176: 11: 1680 – 1685.

71. DiNicolantonio J J, Lucan S C, O'Keefe J H. The evidence for saturated fat and for sugar related to coronary heart disease. Prog Cardiovasc Dis 2016; 58: 5: 464 – 472.

72. Smith T. The cholesterol-heart hypothesis: How public health advice on nutrition may be on the verge of a major paradigm shift. Alban Med J 2014; 2: 7 – 9.

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