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Review Article

The Dietary Fat–heart Disease Hypothesis: An Ongoing Debate

Nasr Anaizi[1]

[1]Department of Physiology, Faculty of Medicine, University of Benghazi, Benghazi, Libya

Abstract

The belief that the consumption of saturated fat as the primary source of daily energy needs is detrimental to heart health has held a firm grip on public consciousness for decades. It was initially based entirely on tenuous observational (correlation) studies but was later bolstered by a vast array of evidence and more direct observations from long-term randomized controlled trials and dietary intervention studies. Further support also came from the elucidation of the pathophysiology and molecular mechanisms involved in atherogenesis. However, in recent years, the association between dietary saturated fat and heart disease has come under attack based mainly on meta-analyses and large multinational studies most of which relying on questionnaires and diet recall. More recent publications have elevated the debate to a new level, leading some experts to question the evidence behind commonly accepted dietary recommendations, attracting media attention, and generating heated debates. Here, the most relevant studies will be reviewed defining the salient issues and where the proponents and opponents of the hypothesis stand.

Keywords: Cardiovascular risk, dietary fat, heart disease

The Hypothesis Early Years

The diet–heart hypothesis links dietary fat, especially the saturated variety, to the incidence of cardiovascular disease (CVD) in general and coronary heart disease (CHD) in particular. The origin of this hypothesis goes back to the 1950s when the physiologist Ancel Benjamin Keys (1904–2004) first developed it. His theory was based solely on observational data that saturated fat is the main cause of CHD-related deaths, which he attributed to the rise in the serum level of total cholesterol (TC) and the buildup of the atherosclerotic plaques characteristic of CHD.[1,2] Despite the skepticism of some statisticians and public health researchers, the theory quickly gained wide acceptance among clinicians and led to the official recommendation by the American Heart Association (AHA) that Americans limit their intake of saturated fat. On the contrary, an alternative theory implicating sugar as the primary culprit did not gain similarly large acceptance.[3] The criticism of Keys' hypothesis was based on a number of issues related to the handling, analysis, and interpretation of the data:

1. Although Keys obtained data from 22 countries, he considered only data from six countries to obtain a cleaner, clearer association (a better-looking graph); he tossed out the data points that did not fit the hypothesis perfectly! However, when his critics analyzed the data from all the 22 countries, the link between fat and CHD-related death remained statistically significant [Figure 1][4]
2. Keys failed to emphasize or at least recognize that a significant association is not in itself proof of a cause-effect relationship. Consequently, he failed to explore the reasons why fat might be linked to heart disease and ignored the potential association between heart disease and the consumption of other macronutrients
3. The availability of animal fat (and protein) is a proxy for the level of prosperity. The amount of saturated fat available for consumption is an index of the country's wealth and advancement regarding education, nutrition, and medical care. Therefore, it is possible that superior medical care might offset a higher consumption of saturated fat
4. Death rates from CHD vary widely across countries and variations in diagnostic coding practices have given rise to doubts concerning the validity of comparisons between countries concerning heart disease-related mortality rates. Differences in the level of advancement in the health-care system are reflected in the accuracy and compliance with

Address for correspondence: Prof. Nasr Anaizi, Department of Physiology, Faculty of Medicine, University of Benghazi, Benghazi, Libya.
E-mail: anaizi1@gmail.com

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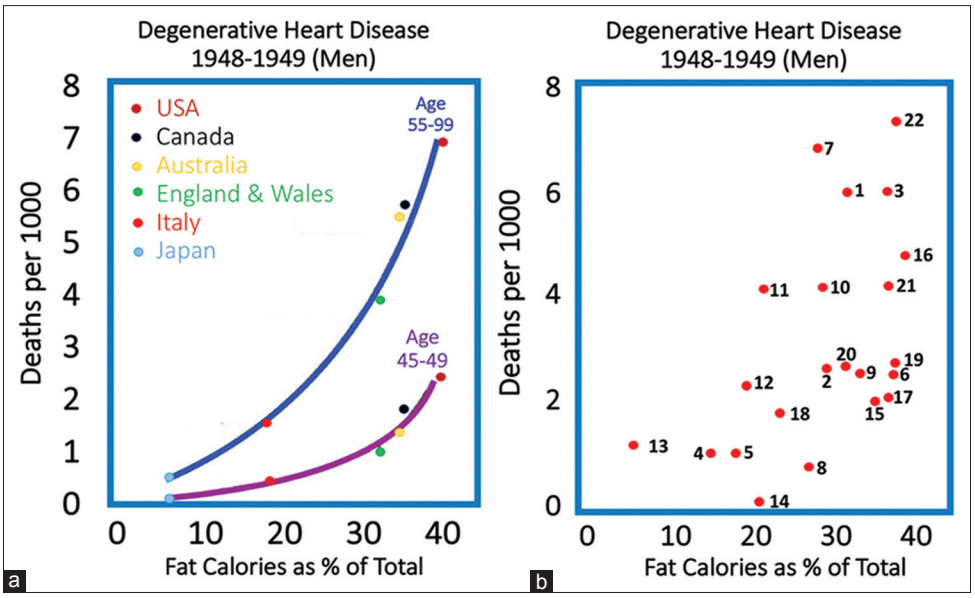

Figure 1: The relationship between heart disease-related mortality and the contribution of fat to the total daily calorie intake: Panel (a) is based on data selected by Keys from the six countries and panel (b) is a similar plot based on Keys data from all the original 22 countries

diagnostic disease classification and coding of mortality. These differences may have contributed to the higher CHD-related death rates reported by the more advanced countries.[5]

As pointed out below, gaps in development and socioeconomics remain major confounding factors that plague large, multinational observational studies and meta-analyses of nutrition data regardless of whether they are for or against the fat–heart hypothesis (lipophobic vs. lipophilic).

Better Evidence

Despite the initial storm of criticism, Keys' theory survived, and the AHA dietary recommendation it generated was incorporated into the US government 1977 Dietary Goals. Eventually, the belief that "saturated fat is bad for your heart" spread worldwide. The durability of this idea does not stem from Keys' original observations, but rather from the subsequent accumulation of evidence.

Effects of dietary saturated fatty acids on plasma lipid profile

Over the past many decades since the 1950s, the link between dietary saturated fat and the plasma cholesterol and lipoprotein profile has been documented by some controlled dietary intervention studies.[6,7] However, a direct and clear link to CHD remained elusive. Furthermore, a few studies appeared to suggest that there is no link at all. A meta-analysis conducted by Siri-Tarino *et al*.[8] considered 21 prospective cohort studies and found no evidence supporting a clear association between the consumption of saturated fatty acids (SFAs) and increased risk of CVD. Similarly, de Souza *et al*.[9] reviewed 12 prospective cohort studies and failed to find a significant relationship between SFAs consumption and CHD-associated mortality. On the other hand, Jakobsen *et al*.[10] demonstrated that replacing the equivalent of 5% of the daily energy needs (5%E) from SFAs with polyunsaturated fatty acids (PUFAs) results in a significant reduction in CHD-related deaths. By contrast, a low-fat high-carbohydrate diet increased CHD risk. Additional evidence was obtained by Li *et al*.[11] based on the results of two large prospective cohort studies, in which 5%E of SFAs was replaced isocalorically with PUFAs or monounsaturated fatty acids, resulting in 25% or 15% reduction in CHD risk, respectively. Similar results were obtained in additional studies, in which PUFAs were used to replace carbohydrates, saturated fat, or trans fat.[12,13] Increased consumption of SFAs raises the plasma level of low-density lipoprotein cholesterol (LDL-C), which is causally linked to atherosclerosis and increased CHD risk. Replacing most of the SFAs in the diet with PUFAs in the form of vegetable oil (linoleic acid) results in markedly reduced LDL-C, TC, TC/high-density lipoprotein cholesterol (HDL-C) ratio, and triglycerides (TG). By contrast, using carbohydrates as the main source of daily calories lowers both LDL-C and HDL-C without affecting the TC/HDL-C ratio, while significantly raising fasting TG level. Just as hypertension is a well-established, independent risk factor for stroke so is elevated serum LDL-C for CHD. The link between a diet rich in saturated fat and other CVD risk factors is also well established.[7] Plasma TGs and the TC/HDL-C ratio, which are considered independent predictors of CVD, are both raised by high SFAs intake. Furthermore, high dietary fat triggers an inflammatory immune response and enhances oxidative stress, thereby promoting LDL-C oxidation (ox-LDL-C), a crucial step in atherogenesis.[14,15] The combination of inflammation and the resultant damage to the endothelial lining of blood vessels lead to endothelial cell dysfunction (ECD) and promote blood clotting. ECD is defined as a deficiency in

the production and bioavailability of endothelial-derived nitric oxide (NO) and the resultant abnormalities in vascular reactivity. In addition to being the most potent endogenous vasodilator, NO is necessary for a number of critical regulatory functions.[16] It inhibits smooth muscle cell proliferation, platelet aggregation, and the adhesion of monocytes to the endothelial cells. ECD is considered an essential pathogenic condition for the development of atherosclerotic CHD. Reduced endothelial NO availability is observed in patients with CVD or coronary risk factors such as hypertension, dyslipidemia, hyperhomocysteinemia, and diabetes.[17]

Recent Challenges

The long-held views regarding the association between saturated fat and CHD were challenged on numerous occasions in recent years. As mentioned above, in 2010 came the meta-analysis of data from over 200,000 individuals who were followed up for at least 5 years. Based on this meta-analysis, the authors concluded that there is no association between dietary saturated fat and CHD.[8] However, upon scrutiny, major methodological flaws and multiple sources of errors were identified which cast doubt on the accuracy of the dietary data.[18] As a result, the conclusions of this meta-analysis were largely rebuffed by the closer scientific community.[7] Interestingly, in the same year in which this controversial meta-analysis was published, a different meta-analysis was also published.[13] However, here, the authors exclusively included randomized controlled trials (RCTs), in which coronary events were reported and where the sole intervention was the replacement of most of the SFAs in the diet with PUFAs for a minimum of 1 year.[13] This meta-analysis included eight RCTs with over 13,000 participants and over 1000 CHD events reported. The PUFA individuals obtained about 15% of their daily energy needs (15%E) from PUFAs compared to about 5%E in the control group. This dietary intervention alone resulted in reducing the CHD risk by 19% or about 10% for each 5%E reduction in SFA intake. This conclusion was supported by comprehensive reviews and additional meta-analyses of all available RCTs investigating the effect of reducing dietary saturated fat on CVD.[10-12,19] These studies demonstrated that replacing the majority of SFAs in the diet with PUFAs significantly decrease the risk of CHD. This effect was particularly evident in the case of fatal CHD.

Minnesota Coronary Experiment

Despite the vast array of concordant evidence from controlled dietary intervention studies, the challenge to the diet-CHD link persists. In 2016, Ramsden *et al*.[20] published an analysis of raw data they obtained from an old, never-published NIH-supported study conducted at the University of Minnesota between 1968 and 1973 and labeled the Minnesota Coronary Experiment (MCE). The data were recovered from the home of Ivan Frantz, the original principal investigator where they were inexplicably abandoned and unutilized for over 40 years. Ramsden *et al*. also made the use of an unpublished master's thesis based on the MCE data. Part of the saturated fat in the diet of the "experimental group" was replaced by corn oil and "polyunsaturated margarine." Based on their analysis of the MCE raw data, Ramsden *et al*. concluded that "Available evidence from RCTs shows that replacement of saturated fat in the diet with linoleic acid effectively lowers serum cholesterol but does not support the hypothesis that this translates to a lower risk of death from CHD or all causes. Findings from the MCE add to growing evidence that incomplete publication has contributed to overestimation of the benefits of replacing saturated fat with vegetable oils rich in linoleic acid."

It was further reported that the greater the lowering of serum cholesterol, the greater the mortality risk. This conclusion runs contrary to the multitude of reports supporting a close association between dyslipidemia (⇑LDL-C + ⇑TC/HDL-C ratio + ⇑apolipoprotein B (ApoB)/apolipoprotein A1 (ApoA1) ratio + ⇑TGs) and heart disease.[6] However, it is possible that the greater cholesterol lowering response (and higher mortality rate) occurred in patients with higher and long-standing baseline hypercholesterolemia and its attending endothelial damage. Furthermore, serum cholesterol level alone, whether TC or LDL-C, is of course of limited use in assessing CHD risk. In addition to ECD, vascular inflammation, and a pro-oxidant milieu, the critical determinants of CHD risk are (a) The LDL/HDL ratio or ApoB/ApoA1 ratio; the higher these ratios are, the higher the risk; (b) the LDL-C particle size; smaller dense particles are associated with a higher risk.

Ramsden's conclusions directly contradict the findings of a large, systematic review and meta-analysis of prospective studies which demonstrated that a higher intake of linoleic acid (an omega-6 PUFA) instead of SFAs is associated with a lower CHD risk.[21]

Possible limitations that may explain the discordant results negating the diet-heart hypothesis include:

a. Incomplete or inaccurate data regarding the quality and/or quantity of the fatty acids in the diet. For instance, in the MCE, no data were reported regarding the trans fatty acids (TFAs) content of either diet. In fact, the diet of the corn oil group included "polyunsaturated margarine" whose TFAs content is uncertain during the period of the study (1968–1973). TFAs are unsaturated fatty acids with one or more C=C double bonds in the trans configuration. It is well established that TFAs intake causes dyslipidemia, impairs endothelial cell function, and increases the risk of CHD[9,22,23]
b. The MCE may have been too short to show the cardiovascular benefits of reducing dietary saturated fat; patients were followed for an average of 15 months only
c. The unsaturated fat in the experimental diet consisted primarily of the omega-6 linoleic acid (18:2*n*−6). Although this diet lowered serum cholesterol, it is highly likely that the LDL-C particles were enriched with linoleic acid and this may have rendered them more susceptible to oxidation, thus promoting atherogenesis.[24] Furthermore,

omega-6 fatty acids are increasingly recognized as being pro-inflammatory.[25] Vascular inflammation is a key factor in promoting the progression of atherogenesis.[26-28] Furthermore, human studies suggest that higher levels of omega-6 PUFAs in cell membranes and lipoprotein particles may promote atherosclerosis by promoting a prooxidant state and enhancing the susceptibility of the atherogenic lipoproteins: very low density lipoproteins and LDL to oxidation, which is an important step in the process of atherogenesis[29,30]

d. Other potential confounders include differences in the individuals' baseline levels of dyslipidemia, inflammation, and endothelial dysfunction. This may explain the observation that a greater drop in serum cholesterol was associated with a higher mortality rate
e. Heterogeneity of study participants in terms of education, socioeconomic conditions, food security, and access to adequate health care. Thus, it is safe to say that the same confounders plague both the opponents and proponents of the diet-heart hypothesis.

The Prospective Urban and Rural Epidemiology Study

Another challenge that generated a flood of sensational headlines such as "Fat and Happy;" "Everyone Was Wrong: Saturated Fat Can Be Good for You;" "Why Saturated Fat Is Not the Enemy.;" or "Saturated Fat-Healthy For Good," came from a more recent prospective study published in the Lancet in August 2017. Briefly, the Prospective Urban and Rural Epidemiology (PURE) study aimed to evaluate the health outcomes associated with variations in diet. It was conducted in 18 countries across the globe from Bangladesh to Canada and including South Asia, Europe, Middle East, South America, and Africa. The study included about 135,000 participants across a wide range of socioeconomic strata, from high to very low. The participants were enrolled as far back as 2003, or as recently as 2013, and were followed for an average of about 7.5 years. For most participants, the dietary intake was assessed once at baseline using a food-frequency questionnaire, and for a small subsample, an additional dietary intake tool, the 24 h diet recall, was used, but the correlation between the two intake tools was poor. The PURE study generated at least three papers which were published virtually simultaneously.[31-33]

The two main conclusions of the PURE study concerning diet and CVD risk are:

1. "Higher fruit, vegetable, and legumes (VFL) consumption was associated with a lower risk of noncardiovascular and total mortality. Benefits appear to be maximum for both noncardiovascular mortality and total mortality at three to four servings per day (equivalent to 375–500 g/day)." The same result was obtained when the data were analyzed on a country-per-country basis[30]
2. "High carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality. Total fat and types of fat were not associated with CVD, myocardial infarction, or CVD mortality, whereas saturated fat had an inverse association with stroke. Global dietary guidelines should be reconsidered in light of these findings."

In other words, a diet high in carbohydrates is associated with a higher mortality rate while a diet rich in fat has no effect on the incidence of CVD or CVD-related mortality. Furthermore, according to the PURE study, saturated fat may specifically lower the risk of stroke.[34]

A third publication generated by the same PURE study suggested that "ApoB-to-ApoA1 ratio probably provides the best overall indication of the effect of SFAs on CVD risk …," and restated the obvious, "focusing on a single lipid marker such as LDL cholesterol alone does not capture the net clinical effects of nutrients on cardiovascular risk."[33] The importance of the apolipoproteins ratio as a risk factor for CVD is well established.[34] ApoA1, a major protein component in HDL particles, is synthesized principally in the liver and in the small intestine. ApoA1/HDL particles transport excess cholesterol from peripheral tissues to the liver. In addition, ApoA1 possesses anti-inflammatory, antioxidant, and antiapoptotic functions. Thus, ApoA1 is strongly antiatherogenic. By contrast, ApoB is strongly atherogenic; it's a component of LDL and transports cholesterol to peripheral tissue. Thus, the ApoB-to-ApoA1 ratio represents a balance between ApoB-rich atherogenic particles and apoA1-rich antiatherogenic particles and has long been regarded as a reliable marker of CVD risk.

The PURE study exemplifies the hazards of pooling diet-health outcome data from participants with vastly different socioeconomic conditions. Participants with the highest VFL intake are better educated, have higher income, more physically active, and are less likely to smoke. Attempting to factor in these differences using a multivariable statistical model tends to dilute the benefits attributed solely to VFL; hence, the VFL benefit reaching an apparent maximum at 3–4 servings per day. The same overall conclusion was reached when comparing different countries; the poorest health outcomes and the lowest VFL intakes were observed in the poorest countries (Bangladesh, Malaysia, Pakistan, and Zimbabwe).

In the PURE study, carbohydrates whether from VFL or from white rice were considered as one category as their contribution to total daily energy requirement (%E) was estimated. This led to the paradoxical observation that while high VFL intake was associated with lower rates of CVD and total mortality, the opposite is true when total carbohydrate was considered. The apparent paradox lies in the fact that VFL is made up mostly of complex carbohydrates including dietary fiber.

Across the countries included in the PURE study, total fat intake ranged from 18%E to 30%E while saturated fat intake ranged from 6%E to 11%E. These figures are far lower than reported for the Western diet in the affluent countries of Europe, Canada, and the US. Again, the socioeconomic factor

looms large with respect to fat versus carbohydrates intake. Participants with the lowest fat intake (and the highest intake of total carbohydrates) are most likely to suffer from food insecurity, low protein intake and generally poor nutrition, and are least likely to have access to adequate health care. Such confounders are too many and too difficult to factor into statistical analyses.

Effect of specific saturated fatty acids on plasma lipid profile

Individual SFAs vary with respect to their effects on specific lipoprotein particles. The chain length of the SFA appears to influence its effect on serum cholesterol. When replacing dietary carbohydrates isocalorically, lauric (12:0), myristic (14:0), and palmitic (16:0) acids raised serum LDL-C, whereas stearic acid (18:0) did not; in this respect, stearic acid is often described as being biologically neutral. The SFAs with 12, 14, and 16 C atoms are the predominant fatty acids in coconut oil, constituting 48%, 16%, and 10%, respectively, of the total fat content of the oil. Evidence in animals and humans indicates that myristic and palmitic acids suppress receptor-dependent cholesterol transport to the liver, increase LDL-C production, and raise the serum LDL-C level. Stearic acid has no effect on the production, transport, or level of LDL-C. By contrast, lauric acid increased TC markedly primarily by increasing HDL-C. All four SFAs raised HDL-C to some extent with lauric acid having the highest effect and stearic acid effect being barely significant. Only lauric acid significantly reduced the TC/HDL-C ratio.[35,36] Thus, while lauric acid appears to improve the plasma lipid profile, coconut oil on the whole does not.

Naturally, contradictory observations and conclusions generate a great deal of media attention[37] and disseminate the notion that saturated fat is harmless, further confusing consumers and health-care professionals alike.[7,18] It is likely that such ideas will continue to circulate in the medical literature, popular press, and in cyberspace, spawning new health claims and diet fads.

It is clear that the link between saturated fat and CVD will continue to be the target for criticism and challenge for years to come. The scientific community will continue to tackle the technical, statistical, and conceptual obstacles that have so far complicated this area of medical research. The path to clarity and scientific satisfaction lies in keeping an open mind and pursuing long-term and more rigorous dietary intervention controlled randomized trials.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

Not required.

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