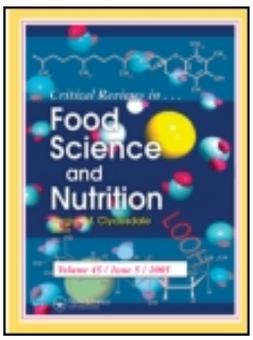

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# Saturated Fats and Cardiovascular Disease: Interpretations Not as Simple as They Once Were

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*Historically, the so-called "lipid hypothesis" has focused on the detrimental role of saturated fats per se in enhancing the risks of cardiovascular disease. Recently, a body of new information and systematic analyses of available data have questioned simple interpretation of the relationship of dietary saturated fats and of individual saturated fatty acids to CVD risk. Thus, current assessments of risks due to dietary fat consumption that emphasize the confounding nature of the dietary macronutrients substituted for dietary saturated fats and give broader recognition to the effect of patterns of food intake as a whole are the most productive approach to an overall healthy diet.*

**Keywords** Lipid hypothesis, palmitic acid, LDL, HDL, cholesterol, PUFA

## *INTRODUCTION*

During the 1940s, Ancel Keys began a series of observations that form the foundation for what has become known as "the lipid hypothesis" (Andrade et al., 2009). Through a series of studies that spanned decades, the most famous of which was his "Seven Countries" study, Keys' observational data led to widespread recommendations for the intake of dietary fats, including Keys' advice in 1959 to "restrict saturated fats" and "prefer vegetable oils to solid fats, but keep total fats under 30% of your total calories" (Nestle, 1995). In the intervening half-century, the literature on the relationships among dietary fats, dietary cholesterol, and cardiovascular disease is surely the most extensive body of observational and interventional data on diet and health in humans ever collected. The historical interpretation founded on these data is to limit the intake of saturated fats because these fats raise LDL cholesterol, itself linked to increased risk of heart disease. Since saturated fats are primarily consumed in animal foods, dairy products, and certain plant oils like coconut and palm oils, dietary guidelines have correspondingly recommended limiting the consumption of red meat, cheese and solid plant fats, including tropical oils. Nonetheless, new data have begun to question simple interpretations of the relationships between the consumption of various dietary fats and risks of consequent cardiovascular diseases.

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## *DIETARY FATS AND CIRCULATING LIPOPROTEINS*

Based on extensive data collected over the last half-century, we have reasonably confident knowledge about the effects of dietary intakes of specific fatty acids on circulating lipids and lipoproteins (Mensink et al., 2003; Micha and Mozaffarian, 2010; Baum et al., 2012). Thus, when replacing dietary carbohydrates, all dietary fats lower blood triglyceride levels, and the effect of saturated fats is approximately the same as mono- and poly-unsaturated fats (Mensink et al., 2003). Conversely, all fats increase HDL-Cholesterol (HDL-C) when replacing dietary carbohydrates and, although the differences are not great, saturated fats increase HDL-C more than mono-and poly-unsaturated fats (Micha and Mozaffarian, 2010; Baum et al., 2012). The increases that result from ingestion of saturated fats do not alter the circulating total cholesterol to HDL-C ratio since ingestion of myristic, palmitic and stearic acids themselves have no significant effect on the TC/HDL-C ratio (Micha and Mozaffarian, 2010). However, the effects of different dietary fats on LDL-cholesterol are divergent. When dietary carbohydrates are replaced by mono- or poly-unsaturated fats, LDL-C declines; but when saturated fats replace carbohydrates, LDL-C increases (Mensink et al., 2003; Micha and Mozaffarian, 2010; Baum et al., 2012). In the latter case, although stearic

acid has essentially no effect on circulating LDL-C levels, ingestion of the saturated fatty acids lauric and myristic produce a greater (and approximately equal) increase of LDL-C, while palmitic acid increases LDL-C to a somewhat lesser degree (Mensink et al., 2003; Micha and Mozaffarian, 2010; Baum et al., 2012). Nonetheless, drawing simple conclusions about the clinical consequences of increasing LDL-C following ingestion of saturated fats is not an entirely straightforward matter. The circulating population of LDL particles is not a homogeneous one. The distribution of LDL subclasses varies among people and is independent of total LDL-C. Small dense LDL particles are those most associated with detrimental cardiovascular disease risk (Griffin et al., 1994; Dreon et al., 1998; Berneis and Krauss, 2002; Siri-Tarino et al., 2010; Hoogeveen et al., 2014; Krauss, 2014). However, the primary effect of saturated fat ingestion on LDL is to raise the level of larger, less dense LDL particles, particles less strongly associated with cardiovascular disease risk (Griffin et al., 1994; Dreon et al., 1998; Berneis and Krauss, 2002; Siri-Tarino et al., 2010a; Hoogeveen et al., 2014; Krauss, 2014).

## *DIETARY FATS AND CARDIOVASCULAR DISEASE RISK*

Given the complexity of the above lipid and lipoprotein responses to ingestion of saturated fats, and given the variable contents and patterns of individual saturated fatty acids in different food sources of saturated fats, there is no simple means of estimating the net clinical consequences of consuming dietary saturated fats by analysis of changes in circulating lipids and lipoproteins alone. Doing so requires human studies with determination of appropriate cardiovascular disease endpoints and a series of recent analyses of the literature have now questioned the long-standing thesis that increased consumption of saturated fats is readily translated into greater cardiovascular risk (Siri-Tarino et al., 2010a; Siri-Tarino et al., 2010b; Siri-Tarino et al., 2010c; Mozaffarian et al., 2010; Astrup et al., 2011; Siri-Tarino, 2011; Sanders, 2012; Lawrence, 2013). In fact, most of the recent assessments have failed to support a direct relationship. For instance the measurement of specific circulating biomarkers has shown that dairy fat consumption does not relate to incident stroke (Yakoob et al., 2014).

Nonetheless, there is an additional complexity inherent in the practical design of such studies. If one aims to maintain an isocaloric diet, one cannot simply change the dietary content of one dietary macronutrient (saturated fat in this instance) without introducing a corresponding opposite change in other contributors to the macronutrient class (unsaturated fats replacing saturated ones) or oppositely altering the content of one of the other macronutrients (carbohydrate, for example). In other words, human studies assessing the effects of dietary saturated fats are, in fact, studies of the consequences of changing food patterns of the whole diet, not simply the consequences of altering dietary saturated fats alone. Conclusions drawn from the studies should be interpreted in the context of the entire dietary pattern, not simply as the consequence of a change in dietary saturated fat. And, even here, the conclusions are often open to multiple interpretations.

Overall, substitution of dietary carbohydrate with saturated fat does not appear to adversely affect CVD risk (Mozaffarian et al., 2010; Siri-Tarino et al., 2010c; Astrup et al., 2011) even though increasing dietary saturated fat raises circulating HDL levels (Siri-Tarino, 2011; Eckel et al., 2013) and lowering dietary carbohydrate load reduces triglyceride levels, small dense LDL particles, and adverse clinical and metabolic markers associated with increased CVD risk (Siri-Tarino et al., 2010a; Eckel et al., 2013; DiNicolantonio, 2014). The overall null conclusion related to dietary carbohydrate intake, however, is compatible with the largely inconsistent results found in a wide variety of studies of the relationship between dietary carbohydrate intake and CVD risk (Rebello et al., 2014), including the failure to find an effect of dietary carbohydrate on ischemic heart disease mortality in an Asian population whose intake of dietary carbohydrates constituted approximately 50–70% of dietary energy intake (Rebello et al., 2014). Even weighing the evidence of reducing the dietary glycaemic index and glycaemic load in preventing diet-related diseases is inconclusive (EFSA, 2010).

Palmitic acid is the principal saturated fat in palm where it does not appear to have a negative effect on the serum lipid profile. Moreover, the particular triacylglicerol conformation in palm oil may lead to absorption of more unsaturated fats than saturated fats (Bester et al., 2010). Also the fine structure of different palm oils may result in different atherogenic effects (Kritchevsky et al., 2002). From these observations we may easily derive that the relationships of palm oil ingestion to detrimental effects, if any, is not simple. This complexity has been shown by an older study, where palm olein, when used as cooking oil, had no detrimental effects on plasma lipid profiles in Malaysian adolescents, leaving unaltered the Apoprotein B / Apoprotein A-I ratio (Marzuki et al., 1991). Accordingly, dietary palm olein seems not to obey the classic Keys-Anderson equation used to predict serum cholesterol responses in humans induced by changes in dietary fats (Keys et al., 1957), being more hypocholesterolemic than predicted when replacing sources of saturated fats such as coconut oil (Ng et al., 1991).

The consequences of substituting unsaturated fats for saturated fats on plasma lipids and lipoproteins are generally agreed upon. Polyunsaturated fat substitution lowers LDL-C, HDL-C and circulating triglycerides (Eckel et al., 2013). Monounsaturated fat substitution lowers LDL-C to a somewhat lesser extent and HDL-C to a somewhat greater extend while increasing circulating triglycerides slightly (Eckel et al., 2013). Extending these changes to beneficial clinical outcomes has become the subject of recent debate.

Because the evidence is insufficient, saturated fat replacement with mono-unsaturated fat appears to have uncertain or little clinical benefit (Jakobsen et al., 2009; Micha and

Mozaffarian, 2010; Astrup et al., 2011). While a significant body of literature supports the conclusion that replacing dietary saturated fats with polyunsaturated fats is associated with a reduced risk of CVD (Jakobsen et al., 2009; Siri-Tarino et al. 2010c; Astrup et al., 2011; Baum et al., 2012; Farvid et al., 2014), there is an accumulating body of literature (Kotwal et al., 2012; Rizos et al., 2012; De Goede et al., 2013; Ramsden et al., 2013; Chowdhury et al., 2014; Ravnskov et al., 2014; Schwingshackl and Hoffmann, 2014), that does not support this position, including a meta-analysis of 32 observational studies with more than 500,000 participants, and 27 randomized controlled trials of more than 100,000 participants (Chowdhury et al., 2014). Overall, a unified simple conclusion is not immediately forthcoming because of heterogeneity of study designs and endpoints as well as the various different limitations of the studies themselves (Baum et al., 2012). The latter citation also highlights one of the earlier interventional trials that included women (Frantz et al., 1989). The Minnesota Coronary Survey study directly tested the substitution of polyunsaturated fat (corn oil and corn oil margarine) for saturated fat and was conducted in more than 9,000 institutionalized subjects, with approximately equal numbers of men and women. The subjects were randomized to diets that differed in saturated fat content by 100% (9 or 18% of energy) and polyunsaturated to saturated fat ratios that differed by a factor of six (0.28 or 1.67). The primary end-points were acute and silent myocardial infarctions and sudden deaths. Nearly five years later there was no statistical difference in any of the primary end-points or in all-cause mortality between the two groups, nor were there any statistically significant differences found on the basis of gender (Frantz et al., 1989).

## *CONCLUSIONS*

What is the practical application message one should extract from this literature? As outlined by others (Astrup et al., 2011; Eckel et al., 2013), the effect of individual foods on coronary heart disease cannot be predicted solely on the basis of their content of saturated fats because individual saturated fatty acids have different cardiovascular effects. Additionally, ultimate effects of dietary interventions on cardiovascular endpoints depend on the precise nature of the dietary macronutrients substituted in place of saturated fats. Moreover, major food sources contain other constituents, such as polyphenols, for instance, that could affect cardiovascular disease risks. For these reasons, one should focus sound nutritional advice on the overall composition of whole diets and the nutrient patterns within those diets rather than focus narrowly on individual foods and/or food components themselves. This conclusion was recently supported by one of the principal scientists in the field, Dr. Frank Hu, who replied when questioned about the latest data questioning the role of saturated fats in heart disease: "The single macronutrient approach is outdated... I think future dietary guidelines will put more and more emphasis on real food rather than giving an absolute upper limit or cutoff point for certain macronutrients" (O'Connor, 2014).

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