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Controversies and discrepancies in the effect of dietary fat and cholesterol on cardiovascular risk

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ABSTRACT Cardiovascular disease (CVD) is the leading cause of death worldwide. The top ten causes of death in Singapore include many cardiovascular-related diseases such as ischaemic heart disease. The increasing prevalence of CVD poses a burden to both the economy and healthcare system of a country. Dietary habits, in particular dietary fats and cholesterol intake, have been shown to greatly influence CVD risks. Therefore, reference and adherence to relevant dietary guidelines could be crucial in CVD prevention. Recent research findings have provided novel insights into the relationship between certain dietary fats or cholesterol intake and CVD risks, challenging or reinforcing previous guidelines. These findings may, however, be conflicting, and there are still controversies over the effects of dietary fats and cholesterol as well as their association with cardiovascular risk. This review paper aims to evaluate common controversies, identify gaps in relevant research areas and summarise evidence-based dietary recommendations.

Keywords: cardiovascular risks, cholesterol, dietary fat, heart disease

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, contributing to 31% of all deaths.[1] The annual number of deaths caused by CVD is expected to rise, from the estimated 17.3 million to 23.6 million by 2030.[2] In Singapore, ischaemic heart disease was the third most common cause of death in 2016. Other CVDs such as cerebrovascular disease and hypertensive heart disease are also among Singapore's top ten causes of death.[3] This increasing prevalence of CVD poses a burden to both the economy and healthcare system of a country.

Numerous studies have demonstrated the significant impact of dietary habits on CVD risks. However, these findings have been conflicting at times, especially for dietary fats and cholesterol intake.[4] Therefore, it is crucial to review dietary guidelines for such nutrients, ensuring the availability of updated information to the public. Such guidelines serve as a reference for healthcare workers and assist policymakers as they tailor-make public health strategies. This review paper aims to consolidate and evaluate some common controversial matters with respect to dietary fats and cholesterol in association with cardiovascular risk, identify gaps in relevant research areas and summarise dietary recommendations based on evidence from research studies.

IS EGG CONSUMPTION ASSOCIATED WITH INCREASED CARDIOVASCULAR RISK?

Historically, it has been assumed that serum cholesterol levels rise with dietary cholesterol, and that CVD risk would consequently rise with increased dietary cholesterol intake.[5] Therefore, the Singapore Heart Foundation (SHF) recommends a 300-mg limit of dietary cholesterol per day.[6] The American Heart Association also sets an upper limit of 300 mg dietary cholesterol per day and intake of three egg yolks per week.[5]

More recently, it was consistently demonstrated that this premise is untrue. The latest 2015–2020 American dietary guidelines removed the upper limits for dietary cholesterol.[7] Multiple cohort studies suggested that dietary cholesterol intake does not significantly affect the incident of CVD risk.[8-11] In cholesterol-feeding studies, it was shown that an addition of 100 mg/day dietary cholesterol would only increase serum cholesterol by 1%–3%. This minute increase in serum cholesterol does not necessarily have much impact on CVD risk.[12]

Eggs are rich dietary sources of cholesterol (200 mg per egg), and numerous studies have focused their investigations on the association between egg consumption and cardiovascular health.[13] Although the SHF still recommends a limit of 3–5 eggs per week for improved heart health, a recent dose-response meta-analysis of six prospective cohort studies actually demonstrated that consuming up to seven eggs per week would not increase cardiovascular risk.[6,13] In another recent randomised, controlled, single-blinded, crossover trial involving 32 adults with coronary artery disease (average age 67 years), no differences were observed in cardiac risk factors, such as serum cholesterol, lipid profile and endothelial function, among three treatment groups (two eggs daily, an egg substitute daily, or no eggs but a high-carbohydrate breakfast daily) over the span of six weeks with a four-week washout period in between each meal plan.[14] However, it was shown in some studies that egg consumption could impact the CVD risk directly in specific subgroups of patients, such as those with chronic diseases and Type 2 diabetes mellitus.[15]

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Possible mechanisms

The lack of association between dietary cholesterol and CVD risk might be due to a metabolic feedback mechanism regulating cholesterol homeostasis, such as different intestinal absorption and hepatic cholesterol synthesis rates.[16,17] Endogenous cholesterol synthesis may be suppressed when dietary cholesterol is increased.[18] Nevertheless, cholesterol metabolism varies from individual to individual. In specific subgroups of patients, egg consumption was shown to be directly correlated with cardiovascular risk.[15] These individuals could be 'hyper-responders' (25% of the population) with differing intestinal absorption and endogenous synthesis rates from the rest, resulting in unusually high circulating low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels.[19,20]

Furthermore, particular attention needs to be paid to people with diabetes mellitus and dietary cholesterol consumption.[21] A recent meta-analysis suggested that although egg consumption has no effect on CVD risk among healthy people, people with diabetes mellitus have a 69% greater possibility of experiencing CVD when consuming ≥ 1 egg per day.[22] In the Health, Ageing and Body Composition Study, diets of adults aged 70–79 years were assessed using a food frequency questionnaire. It was observed that consuming ≥ 3 eggs per week could increase the risk of Type 2 diabetes mellitus patients having a fivefold incidence of CVD.[23] In an analysis of First National Health and Nutrition Examination Survey data, 349 people with diabetes mellitus, with an age range of 25–75 years (during baseline), showed higher risk of myocardial infarction when consuming > 6 eggs per week during a 20-year follow-up period.[24]

Evaluation of evidence and our recommendation

The majority of studies on the association between egg consumption and cardiovascular risk have been observational, and there may have been unadjusted confounders. Some studies observed that men who consumed more eggs had less healthy lifestyles, including increased smoking frequency, less physical activity and less ideal eating habits, such as consuming more red and processed meat or less fruits and vegetables.[25,26] Nevertheless, most studies showed no association between dietary cholesterol and CVD risks, suggesting that dietary cholesterol intake may not be directly linked to serum cholesterol in the general population.

Although there is insufficient evidence of an upper dietary cholesterol limit for the general population, certain populations such as individuals who are 'hyper-responders' and those with Type 2 diabetes mellitus should consider limiting eggs and dietary cholesterol and consider more frequent serum monitoring, as they may be more susceptible to fluctuations in serum lipid levels.

ARE ALL FORMS OF TRANS FAT EQUALLY DETRIMENTAL TO CARDIOVASCULAR RISK?

Compared to dietary cholesterol, trans fat (TF) limits have been more stringent and evidence based.[27-31] In Singapore, Agri-Food and Veterinary Authority of Singapore regulations state that fats and oils used in food manufacturing and preparation or for sale should not exceed 2% TF.[32] Increased TF intake has been consistently associated with increased cardiovascular risk, including both fatal and non-fatal myocardial infarction.[33,34]

Possible mechanisms

Several studies showed that increased TF intake could affect lipid and lipoprotein profile, resulting in higher LDL cholesterol, total cholesterol-HDL cholesterol ratio and lower HDL cholesterol, all of which are CVD risk factors.[35,36] Trials have suggested that higher dietary TF intake could either raise cholesteryl ester transfer protein (CETP) activity or reduce CETP inhibitor activity, thereby increasing the cholesteryl esters transferred from HDL to LDL.[37] There may also be other postulated mechanisms related to inflammatory pathways, involving interleukin 6 and C-reactive protein.[38-40] These inflammatory markers contribute to all stages of atherosclerosis development and plaque formation.[41-44]

Industrial TF (iTF) has also been associated with increased CVD risk compared to ruminant TF (rTF). iTF is from industrially manufactured partially hydrogenated vegetable oil in food sources such as margarine, baked products and deep fried foods.[45] rTF is produced naturally when anaerobic bacteria metabolise polyunsaturated fats (PUFA) in the rumens of ruminants, and is usually found in beef, lamb and dairy products.[46] There has been no convincing association between rTF and CVD risks.[46]

Evaluation of evidence and our recommendation

Evidence suggesting a direct association between total TF or iTF and CVD risks has been consistent but does not apply to rTF. While TF restrictions have been implemented in Singapore, efforts could be focused on improving adherence to the TF intake limit. According to the 2010 National Nutrition Survey, three out of ten Singaporeans still exceed the World Health Organization's recommended TF intake limit.[47] This may be in part due to misleading TF nutrition labels. Even products with labels that indicate 'TF free' may be allowed < 0.5 g of TF per serving by certain governing bodies such as the United States Food and Drug Administration.[48] With serving sizes being reduced, individuals might end up consuming a considerable amount of TF despite consuming only 'TF free' products. While there has not been any controversy in research findings, the requirements for the 'TF free' label are of concern, as such labels may negatively influence the population's TF intake. Such bans have consistently demonstrated positive results in improving cardiovascular health at a population level.[49]

SHOULD WE LIMIT ALL TYPES OF SATURATED FATS?

Some guidelines have limited saturated fat (SF) intake to up to 10% of total calories.[50,51] In Singapore, the SHF also recommends that SF intake be less than one-third of total daily fat intake (≈ 10% daily total calories).[52] However, studies on this topic have produced conflicting results. Early studies from 1986 showed that increased SF intake could lead to higher serum cholesterol levels, raising the risk of coronary heart disease (CHD).[53] Similar results were observed from other studies such as the Honolulu

Heart Program, Framingham Heart Study and Lipid Research Clinics Prevalence Follow-up Study.[9,54-56]

On the other hand, more recent studies demonstrated no significant associations between SF and cardiovascular risk. In 2017, the PURE (Prospective Urban Rural Epidemiology) study showed no significant association between SF intake and risks of major CVD, myocardial infarction and CVD mortality.[57] Higher SF intake was even linked with lower risk of stroke.[57] The differences in these findings may be multifactorial. Older studies had focused on European and North American diets, which already had excessive SFs (20% of total energy intake). The PURE study instead considered diets of populations from high-income, middle-income and low-income countries. This might provide a more comprehensive analysis and a better reflection on the relationship between SF intake and CVD risks, as SF intake varies significantly (2%–15% of total energy intake) among different populations.[57]

In addition, a recent meta-analysis involving 21 prospective epidemiologic studies showed no association between SF and CVD/CHD risks.[58] The type of nutrients replacing SFs during SF reduction could also play a crucial role in influencing CVD/CHD risks.[59] CVD risk remained unchanged if SFs were replaced by carbohydrates.[35,60] However, when PUFA replaced SFs, CVD risk was reduced.[61,62] Lower CVD risk might be attributed to not only SF reduction but also the increase in PUFA.[63]

Possible mechanisms and specific subtypes

Not all SFs have the same influence on CVD risks. Different SF chain lengths could result in varying effects on serum cholesterol levels. Consuming long-chain SFs (12:0–18:0) was directly related to CHD, while short- or medium-chain SF intake (4.0–10.0) was not.[64-66]

The food source from which the SFs originated may also be of importance. SFs from meat were directly associated with higher CVD risks and SFs from dairy products with lower CVD risks, whereas SFs from butter and plant sources had no effect on CVD risks.[67-72] One underlying mechanism might be the blood-pressure-lowering effect of oligopeptides produced when probiotic bacteria hydrolyse milk proteins, which inhibit ACE activity, preventing the conversion of angiotensin I to angiotensin II.[73] Minerals found in milk, such as calcium, potassium and magnesium, may contribute to the reduction in blood pressure as well.[74] SFs from butter may have higher HDL-mediated cholesterol efflux capacity that compensates for any LDL-cholesterol-raising effects from butter, resulting in a neutral association between butter and CVD risks.[75] The main sources of SFs from plants are coconut oil and palm oil. Besides SFs, palm oil also consists of oleic acids (monounsaturated) and linoleic acids (LAs; polyunsaturated), and vitamins A and E (antioxidants), which have cardioprotective properties.[76,77] Although lauric acid (C12:0), the main SF in coconut oil, increases LDL cholesterol the most among other long-chain SFs, it raises HDL cholesterol concentration the most as well, hence reducing the total cholesterol-HDL cholesterol ratio.[78,79] These factors might contribute to the lack of association between SF from plant sources and CVD risks.

While increased carbohydrate intake result in lower LDL cholesterol compared to SF intake, it could also lead to lower HDL cholesterol as well as an increase in triglycerides, total cholesterol-HDL cholesterol ratio and apolipoprotein B-apolipoprotein A1 ratio.[57] This might be one reason for the lack of improvement in CVD risks when carbohydrates replace SFs. The quality and glycaemic index of carbohydrate plays a role in its impact on CVD risks as well. Whole grains, when used to replace SFs, have a more positive effect on CVD risks compared to refined sugars.[59]

SF-rich red and processed meats are associated with higher CVD risks in some studies.[80] Various nutrient components of red and processed meats, other than SFs, could have contributed to the increased risks. Higher sodium content in processed meat could raise blood pressure, thereby increasing CVD risks;[81] while nitrates and their derivatives could be associated with oxidative stress, leading to endothelial and vascular dysfunction and hence, raising CVD risks as well.[82] In red meat, heme iron could result in the formation of the highly reactive hydroxyl radical, which plays an important role in LDL cholesterol oxidation.[83] Additionally, heme iron and zinc are directly related to C-reactive protein, an inflammatory marker that may promote atherosclerosis development.[84]

Evaluation of evidence and our recommendation

The association between SFs and CVD risk depends on a number of factors, including the length of the fatty acid chain. Recommendations and limits in the future could target an overall diet change instead of dietary guidelines for SF alone.[85] Dietary SF recommendations could focus on limiting certain SF-rich food sources such as red and processed meat. Consumption of refined carbohydrates to replace SFs during SF reduction should be curtailed. It is reasonable to encourage the replacement of SFs with PUFA intake.

ARE MONOUNSATURATED FATTY ACIDS BENEFICIAL?

Guidelines on the intake of monounsaturated fatty acids (MUFAs) have been vague and variable. MUFAs have often been estimated to be 15%–20% of energy intake.[86] Some organisations have had no specific recommendations for MUFA intake, while in Singapore, the SHF recommends that total unsaturated fatty acids contribute two-thirds of total daily fat intake, with total daily fat intake not exceeding 30% of total energy intake.[52,87]

When MUFA intake is increased to replace excessive SF intake in an isocaloric manner, CAD risks could potentially be lowered by approximately 10%.[88] However, these findings were not consistently demonstrated in all studies.[89,90] The PURE study, a large epidemiological cohort study, found no significant association between MUFA and CVD risk.[57] When comparing the different food sources of MUFA, a recent prospective cohort study showed that only plant-based MUFAs, and not animal-based MUFAs, lower CHD risk significantly.[91] Olive oil, in particular, has been associated with protective cardiovascular benefits.[92]

Possible mechanisms

The CAD risk-lowering effects of MUFA observed when MUFA intake replaces saturated fatty acid (SFA) intake could be due to several possible mechanisms, such as the improvement in serum lipid/lipoprotein profile and lowering of blood pressure.

Previous studies showed a decrease in LDL and total cholesterol levels when MUFAs replace SFA in diets.[93] MUFA is also better at retaining HDL cholesterol levels than PUFA, when comparing the replacement of SFA with either MUFA or PUFA. In a two-way randomised controlled trial, HDL cholesterol levels were lowered by only 4% when MUFA replaced SFA in diets, much less than the 14% HDL cholesterol reduction observed when PUFA replaced SFA.[94] There would be an overall decrease in the total cholesterol-HDL cholesterol ratio. This favourable change in lipid/lipoprotein profile could potentially lower CVD risks.[95]

There is evidence that MUFAs, especially oleic acid in olive oil, show hypotensive effects as well. One possible mechanism could be oleic acid's ability to regulate the structure and composition of lipids and G proteins in cell membrane. This could potentially influence the adrenergic receptor signalling pathway, increasing vasodilatory stimuli (cAMP and protein kinase A) production and limiting vasoconstriction pathways (inositol-trisphosphate, Ca2+, diacylglycerol and Rho kinase).[96,97]

Evaluation of evidence and our recommendation

The PURE study challenged some of the findings from previous studies. Its limitations include the inability to estimate fatty acids found in certain foods from countries such as Malaysia and Zimbabwe. Nevertheless, the merits of the study might outweigh its limitations, as it provided data from a wider range of populations with participants from various demographic backgrounds.[57] As it stands, evidence for the association between MUFA intake and CVD risk remains unclear. Traditional dietary guidelines advocating the benefits of low-fat diets have been based on the assumption from controlled feeding trials that increased dietary fat intake was associated with increased serum cholesterol and that consequently, increased serum cholesterol was associated with increased cardiovascular risk.[98] The large PURE study challenged that fundamental assumption and demonstrated that not all forms of dietary fat were responsible for increasing cardiovascular risk. The CHD risk-lowering effects of plant-based MUFA could be partially contributed by other residual confounding factors, such as dietary fibre, polyphenols and minerals found in plants. Animal-based MUFAs, on the other hand, are often found in food sources such as red meats and dairy products, which are also rich in SFA.[91] Overall, a significant difficulty in designing such dietary studies and guidelines comes from the fact that MUFAs are rarely consumed in isolation. Dietary guidelines could instead focus more on limiting or encouraging the consumption of specific food products and diets, instead of limiting specific nutrients. In the case of MUFAs, dietary fat derived from olive oil may be beneficial compared to those from animal sources.

IS THERE A ROLE FOR N-6/N-3 POLYUNSATURATED FATTY ACIDS IN CARDIOVASCULAR HEALTH?

PUFAs are a group of fatty acids that were shown to have cardioprotective effects. They mainly comprise n-6 PUFAs such as linoleic acid (LA) and n-3 PUFA. n-3 PUFAs are further classified into plant-derived alpha-linolenic acid (ALA) as well as marine-derived eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[99] Lower CVD risks have been observed among populations that consume more fish, such as Alaska Natives, Greenland Eskimos and the Japanese. Fishes, especially fatty fishes such as salmon and herring, are rich in EPA and DHA, containing up to 2,000 mg EPA and DHA per 100 g.[98,100] The cardiovascular benefits of PUFAs may be mediated by altering the lipid profile, inhibiting inflammation and platelet aggregation.[101-103] Additionally, n-3 PUFAs have been useful in secondary prevention of atherosclerotic cardiovascular disease. Following myocardial infarction, patients with higher PUFA intake (mainly from marine sources) showed significantly lower mortality and less recurrence of cardiovascular events such as myocardial infarction or stroke.[104-107] While EPA and DHA intake (from marine sources) consistently show cardiovascular benefit, plant-based PUFAs (mainly ALA) may also lower cardiovascular risk, but studies on the latter show conflicting findings.[108-110]

Possible mechanisms

The underlying mechanism and conceptual importance of the n-6/n-3 ratio stems from the competitive conversion of ALA to the more bioactive EPA and DHA. However, the enzyme, which is more specific for ALA, may be competitively inhibited by n-6 PUFA (dietary LA) if it were in abundance. This would limit the *in vivo* conversion of ALA to EPA and thus limit its cardioprotective effects.[111,112] A lower n-6/n-3 ratio would thus be beneficial, and dietary strategies have been aimed at decreasing n-6 PUFA while increasing n-3 PUFA.

A large randomised trial, OPTILIP, was designed to examine the optimal n-6/n-3 ratio by comparing diets with an n-6/n-3 PUFA ratio of between 3:1 and 5:1 with a control of 10:1. However, the findings revealed no treatment effects and thus no effect on insulin sensitivity, haemostatic function, plasma post-heparin lipase activities or serum lipid profile.[113] The authors postulated that the *in vivo* conversion of ALA to EPA and DHA may only occur to a limited extent and, therefore, the effect of differing n-6/n-3 ratios may not have been significant. Instead of the ratio, absolute amounts of n-6 PUFA and ALA (n-3 PUFA) may be more important. Goyens et al demonstrated that lowering LA (n-6) aided in the synthesis of EPA, while increasing ALA promoted the conversion of EPA to DHA.[114]

Evaluation of evidence and our recommendation

The cardioprotective effects of EPA and DHA are supported by strong evidence.[115,116] Fish and marine sources are particularly important for this nutrient.[117] Based on current evidence, the recommended EPA and DHA intake could be approximately 300–600 mg per day for primary prevention of CVD and about 900–1,200 mg per day for secondary prevention.[118] Instead of focusing on the n-6/n-3 ratio, enhanced conversion of ALA to long-chain n-3 PUFAs may instead by achieved by decreasing the absolute amount of dietary LA and increasing the absolute amount of dietary ALA.

CONCLUSION

Diet, particularly dietary fats and cholesterol intake, plays an important role in altering CVD risks. Studies on certain nutrients, such as TF, showed strong evidence for increasing CVD risks. However, findings on dietary cholesterol, MUFAs and SFs are still conflicting or unclear. Individual responses to dietary cholesterol should be monitored, as they are often variable. Food sources of dietary fats and cholesterol are also important considerations, and food-based recommendations and restrictions may be more practical than nutrient-specific limits. Instead of the n-6/n-3 PUFA ratio, lowering absolute levels of LA and increasing dietary ALA may be helpful. Overall, appropriately controlling dietary fat and cholesterol consumption may help to lower both the social and economic burden of CVD.

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