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## Conference on 'Dietary strategies for the management of cardiovascular risk'

# Dietary cholesterol, heart disease risk and cognitive dissonance

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In the 1960s, the thesis that dietary cholesterol contributes to blood cholesterol and heart disease risk was a rational conclusion based on the available science at that time. Fifty years later the research evidence no longer supports this hypothesis yet changing the dietary recommendation to limit dietary cholesterol has been a slow and at times contentious process. The preponderance of the clinical and epidemiological data accumulated since the original dietary cholesterol restrictions were formulated indicate that: (1) dietary cholesterol has a small effect on the plasma cholesterol levels with an increase in the cholesterol content of the LDL particle and an increase in HDL cholesterol, with little effect on the LDL: HDL ratio, a significant indicator of heart disease risk, and (2) the lack of a significant relationship between cholesterol intake and heart disease incidence reported from numerous epidemiological surveys. Over the last decade, many countries and health promotion groups have modified their dietary recommendations to reflect the current evidence and to address a now recognised negative consequence of ineffective dietary cholesterol restrictions (such as inadequate choline intake). In contrast, health promotion groups in some countries appear to suffer from cognitive dissonance and continue to promote an outdated and potentially hazardous dietary recommendation based on an invalidated hypothesis. This review evaluates the evidence for and against dietary cholesterol restrictions and the potential consequences of such restrictions.

**Dietary cholesterol: Nutrition research methods: Eggs: Heart disease risk**

### The development of a hypothesis

In 1968, the American Heart Association added a recommendation to restrict dietary cholesterol to <300 mg/d to its dietary guidelines for those at high risk for heart disease, and recommended a specific restriction on egg consumption to no more than three whole eggs per week[1]. There are two interesting points regarding these recommendations. First, there was no scientific rationale or justification for selecting 300 mg/d as the limit for dietary cholesterol (other than that the average US intake at the time was 580 mg/d and that 300 mg/d would represent a significant decrease in consumption). Second, of all the dietary recommendations, the egg restriction was the only food-specific restriction in the set of recommendations made by the American Heart Association. Understandably, it was difficult in 1968 to discuss the various dietary sources of total and saturated fats since consumers had little knowledge on this issue and nutrition facts panels had not yet been added to every food item. The semantic relationship between dietary cholesterol and serum cholesterol (i.e. 'cholesterol in food equals cholesterol in the blood') was a concept that could be simply expressed to the general public and would in effect encourage people to reduce animal products in the diet which happened to be the most significant sources of dietary saturated fat, with one exception … the egg. While high in cholesterol, the egg contains a relatively modest 1·5 g saturated fat per 50 g egg. One of the consequences of this focus on dietary cholesterol and eggs was that the egg became the icon for both high dietary cholesterol and high blood cholesterol and, even if the evidence for this relationship was weak, the message was simple and easily conveyed by health professionals not only to their patients at high risk for heart disease but also to the general public.

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Once the dietary cholesterol and egg restrictions became part of the 'Prudent Diet' approach to heart disease prevention, there was little room for argument or questioning of the policy, even from a scientific or research perspective. There were a number of outspoken critics of these early dietary cholesterol and egg guidelines, but for the most part the naysayers were marginalised and discounted (for a fascinating history of the diet–heart disease battles see *Good Calories, Bad Calories* by Gary Taubes[2]). For many sceptics in the scientific community, the dietary cholesterol raises blood cholesterol increasing heart disease hypothesis went from a thesis needing to be proven to a fact which now required application of reverse onus (i.e. now it needed to be proven that dietary cholesterol did not cause heart disease) which was an insurmountable obstacle and mostly set aside in favour of more achievable objectives. It has taken 50 years of research to undo the effects of those early condemnations and the 'cholesterolphobia' much of the world suffered from for decades.

The undoing of this hypothesis has come about through advances in both our understanding of the intricacies involved in the diet–heart disease relationship and through research progress in more precisely defining the various risk factors for heart disease and how they are affected by dietary factors. As in all studies of the relationships between diet and health, the same three lines of evidence used to establish the dietary cholesterol restriction were used to test the validity of the dietary cholesterol–heart disease relationship: animal model studies, analysis of epidemiological survey data and clinical interventions.

### *Animal model studies*

Feeding cholesterol to rabbits results in pronounced dyslipidaemia and the development of atherosclerosis[3]. Feeding cholesterol to a dog or rat has little, if any, effect on plasma cholesterol levels. To develop hypercholesterolaemia in some primate species it is necessary to feed the human cholesterol equivalent of 3000 mg/d. The majority of animal species, when fed a physiologically meaningful amount of cholesterol in the diet, experience little change in their plasma cholesterol profile due to appropriate metabolic feedback mechanisms. When cholesterol is fed, endogenous cholesterol synthesis is suppressed and bile acid synthesis and excretion is increased[4]. These compensatory mechanisms are sufficient to maintain a steady-state level of plasma cholesterol with no change in atherosclerotic risk. Thus, the quandary becomes which animal model best mimics the human condition. Many investigators would contend that probably no animal model best mimics the human response to dietary cholesterol for a number of reasons: differences in the plasma lipoprotein profile, differences in the factors involved in lipoprotein remodelling, species differences in the tissue distribution of endogenous cholesterol synthesis and sterol excretion patterns, variations in plasma metabolism and remodelling of the various lipoproteins and differences between species in the response to other dietary factors[5,6]. For virtually all animal species, intake of physiological levels of cholesterol has no measurable effects on plasma cholesterol levels or CVD development. Animal model studies can make significant contributions to our knowledge of the processes of atherogenesis, but have very limited value in modelling CVD risk factor responses to dietary factors.

### *Epidemiological survey data*

In 1968, the use of simple correlation analyses showed that both dietary cholesterol and dietary saturated fat were related to elevated plasma cholesterol levels and heart disease risk. Unfortunately, since both are found in animal products, they are significantly related to each other. Analysis of epidemiological survey data using multivariant analysis indicated that while saturated fat was independently related to heart disease risk, the significant relationship for dietary cholesterol was lost once the covariance with saturated fat was accounted for[7,8]. As noted by Ravnskov[9], in eleven reports from the prospective and retrospective epidemiological studies there were no differences in dietary cholesterol intakes between cases and controls. And when applied to eggs, which have high cholesterol content but are relatively low in saturated fat, there was no significant relationship between egg intake and heart disease risk. Across cultures there is no significant relationship between *per capita* egg intake and CVD mortality rates[10,11].

A number of studies have looked specifically at the relationship between egg consumption and either plasma cholesterol levels or heart disease risk within populations[12–19]. These studies have consistently shown that egg intake is not related to either plasma cholesterol levels or to heart disease risk in men or women[20,21]. In these studies, the relative risk for CHD was the same whether one ate one egg a week or one egg a day. These findings are consistent with the body of epidemiological analysis reporting that dietary cholesterol is unrelated to heart disease risk within populations[10,11,22]. Recent studies investigating the effects of dietary lipids on subclinical atherosclerosis have also reported the absence of a relationship between dietary cholesterol intakes and mean carotid intimal medial thickness[23].

In a recent meta-analysis of prospective cohort studies on the relationship between egg intake and CHD (3 081 269 person years, 5847 cases) and stroke (4 148 095 person years, 7579 cases), Rong *et al.*[19] reported that there was no evidence of an association between egg consumption and risk of CHD or stroke ($P$=0·67). The relative risk of CHD for an increase of one egg consumed per day was 0·99 and for stroke 0·91. Simply put, analysis of decades of epidemiological data fails to find a relationship between egg intake and heart disease risk.

### *Clinical interventions*

In the early days of metabolic ward studies on the effects of dietary factors on plasma cholesterol levels, patients were often fed liquid formula diets which allowed the

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researchers more precise control over the fat and cholesterol composition of test diets. Unfortunately, this new degree of control led many researchers to develop dietary cholesterol challenges that used pharmacological (rather than physiologically relevant) doses of 1000–4000 mg/d added to liquid diets with 40 % energy as coconut oil. This, of course, resulted in increased plasma cholesterol levels as the endogenous cholesterol metabolic capacity was overwhelmed and the normal feedback regulatory mechanisms failed to compensate[24,25]. In addition, virtually all of the earlier studies used to justify the dietary cholesterol restriction used total plasma cholesterol levels as the surrogate marker for assumed changes in heart disease risk.

As the pattern of research studies shifted from formula feeding to solid foods and more rational, and physiologically relevant, cholesterol intakes, and the measured variables shifted from total to lipoprotein cholesterol levels, the evidence supporting the atherogenicity of dietary cholesterol progressively weakened. However, a consistent finding from study after study was the high degree of variability in plasma cholesterol responses to dietary cholesterol challenges between patients[24]. In order to explain this variability, and its significance in the dietary cholesterol – heart disease question, it is necessary to consider the inter-individual differences in cholesterol metabolism.

Cholesterol synthesis is a function of body weight, approximately 12 mg/kg-d. Therefore, changes in plasma cholesterol with the same dietary cholesterol challenge will differ for individuals having different body weights. Studies also indicate that the fractional absorption rate for cholesterol is highly variable, ranging from 20 to 80 %, with an average of 55 %[26]. Based on these considerations, it is easy to understand why feeding an additional 500 mg cholesterol to a 100 kg male with a fractional absorption rate of 20 % will have a very different effect on plasma cholesterol levels as compared with the effects of the same dietary cholesterol challenge to a 50 kg female with an absorption rate of 80 %. Only a limited number of cholesterol feeding studies have adjusted for differences in body weights and fractional absorption rates between patients[24,26]. Numerous analyses have shown that the average weight-adjusted plasma cholesterol response to a 100 mg/d increase in dietary cholesterol in a 70 kg individual is an increase in plasma total cholesterol of 2·4 mg/dl (0·062 mM/l) with increases in both the LDL cholesterol (1·9 mg/dl, 0·049 mM/l) and HDL cholesterol (0·4 mg/dl, 0·010 mM/l)[25,27–30]. These studies indicate that while adding cholesterol does have a small effect on plasma cholesterol levels, there is little if any change in the LDL:HDL cholesterol ratio, which is also an important determinant of CVD risk[31–33]. Data also indicate that the changes in LDL cholesterol levels with cholesterol feeding are not due to changes in the number of LDL particles, but rather due to changes in the cholesterol content of these particles. Therefore, cholesterol feeding results in less-atherogenic large, buoyant LDL[34] rather than the more atherogenic small, dense LDL particles[35]. With little effect on the LDL:HDL cholesterol ratio[36,37] or on LDL particle number[38] in both responders and non-responders to dietary cholesterol, dietary cholesterol has little effect on CVD risk, as documented by various epidemiological survey analyses[20,21].

## Do no harm

Restricting affordable, high-quality, nutrient-rich foods such as eggs from the diet because of their cholesterol content is not risk free. Affordable sources of high-quality animal protein in the diet, especially foods such as eggs that are widely available and easy to cook, chew and digest, are of significant importance for growth and development as well as for maintaining lean muscle tissue mass in the elderly[39]. Eggs are also an excellent source of choline[40], an essential nutrient that has been shown to be inadequate in the diets of most adults in the USA[41]. Choline plays an important role in fetal and neonatal brain development[42] and inadequate choline intake during pregnancy increases the risk for neural tube defects such as spina bifida[43,44]. Choline intake is also associated with decreased plasma levels of homocysteine and inflammatory factors, both of which are related to increased CVD risk[45,46].

Recent studies have reported negative relationships between dietary choline and breast cancer incidence and mortality as well as a relationship between egg intake and reduced breast cancer risk[47,48]. Data from the Nurses' Health Study indicated that women who had, during adolescence, a higher consumption of eggs had a significantly lower risk of breast cancer later in life[49]. Another study[50] reported data from a case – control study of breast cancer incidence showing that egg consumption was significantly inversely associated with risk of breast cancer. The epigenetic effects of choline availability during prenatal and postnatal development are just beginning to be investigated[51,52].

Eggs also provide highly bioavailable forms of the xanthophylls lutein and zeaxanthin, which are related to lower risks for age-related macular degeneration and cataracts[53–56] as well as some types of cancer[57–59] and carotid artery atherosclerosis[60]. Eggs also provide satiety in the diet[61] and can be a valuable addition to a low-energy weight-loss diet[62].

Restricting eggs in the diet can have negative consequences; and based on the available data, provides little benefit in terms of CVD risk reduction. It is essential that any food's value to health promotion/disease prevention be based on the totality of its nutrients and not just a single component.

## Summary

For over 40 years the scientific community has debated the dietary cholesterol–blood cholesterol relationship and the rationale for restricting high-cholesterol foods, such as eggs, in the diet. Epidemiological surveys show that there is no relationship between dietary cholesterol

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intakes and either blood cholesterol levels or CVD risk between or within populations[19–21]. The only group in which CVD risk has been associated with increased egg intake is the subpopulation with type II diabetes[13,15,63]; however, this may relate to the degree of diabetic control in the study population, a factor that has not yet been controlled for in any of the published studies. Until this question is resolved there is justification in recommending that patients with type II diabetes limit their egg intake to <6 per week based on the available data.

Clinical studies form the basis of continued dietary cholesterol restrictions in some populations based on dietary cholesterol induced changes in total plasma cholesterol levels. However, considering the evidence that dietary cholesterol intake does not affect the LDL: HDL cholesterol ratio[33] or the number of LDL particles[34], the change in total cholesterol levels does not reflect change in CVD risk. When the specific effects of dietary cholesterol on the atherogenicity of the plasma lipids is fully analysed, there is no conflict between the lack of effect of dietary cholesterol on CVD risk observed in epidemiological surveys and the small change in plasma cholesterol levels observed in clinical feeding studies.

The lack of evidence for a relationship between dietary cholesterol and heart disease risk is why most countries of the world do not specifically recommend dietary cholesterol restrictions[64–66]. In fact, in Canada and Australia, eggs carry the approval marking of their respective heart associations. Eggs provide several important nutrients that contribute to health promotion and disease prevention. First and foremost, eggs are an affordable source of high-quality protein, which for too many in the world is not a readily available nutrient due to either availability or prohibitive expense. For the elderly eggs are easy to cook, chew and digest and high-quality protein intake is related to a reduced rate of sarcopaenia[38]. Eggs can also play an important role in weight management due to their satiety effects[66]. Eggs are a major source of choline, a nutrient that has been shown to be inadequate in the diet probably due to both egg restrictions and reduced overall fat intakes in many populations. Over the last two decades studies have shown the importance of choline in health promotion ranging from fetal brain development and epigenetics to reduced breast cancer morbidity and mortality. Eggs contain highly bioavailable xanthophylls important in eye health as well as other important health issues ranging from cancer to CVD[66]. Given the available evidence, there is little rationale for recommending egg restrictions to the public. In fact, it seems that the only health risks associated with egg consumption are those associated with unnecessary and ineffectual restrictions on egg intake.

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## Conflicts of interest

The author is the sole administrator of Eggs for Health Consulting which advises international egg associations on matters related to eggs and health issues.

## Authorship

The author is solely responsible for all aspects of this paper preparation.

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