

Review

Dietary cholesterol and atherosclerosis

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Abstract

The perceived relationship between dietary cholesterol, plasma cholesterol and atherosclerosis is based on three lines of evidence: animal feeding studies, epidemiological surveys, and clinical trials. Over the past quarter century studies investigating the relationship between dietary cholesterol and atherosclerosis have raised questions regarding the contribution of dietary cholesterol to heart disease risk and the validity of dietary cholesterol restrictions based on these lines of evidence. Animal feeding studies have shown that for most species large doses of cholesterol are necessary to induce hypercholesterolemia and atherosclerosis, while for other species even small cholesterol intakes induce hypercholesterolemia. The species-to-species variability in the plasma cholesterol response to dietary cholesterol, and the distinctly different plasma lipoprotein profiles of most animal models make extrapolation of the data from animal feeding studies to human health extremely complicated and difficult to interpret. Epidemiological surveys often report positive relationships between cholesterol intakes and cardiovascular disease based on simple regression analyses; however, when multiple regression analyses account for the colinearity of dietary cholesterol and saturated fat calories, there is a null relationship between dietary cholesterol and coronary heart disease morbidity and mortality. An additional complication of epidemiological survey data is that dietary patterns high in animal products are often low in grains, fruits and vegetables which can contribute to increased risk of atherosclerosis. Clinical feeding studies show that a 100 mg/day change in dietary cholesterol will on average change the plasma total cholesterol level by 2.2–2.5 mg/dl, with a 1.9 mg/dl change in low density lipoprotein (LDL) cholesterol and a 0.4 mg/dl change in high density lipoprotein (HDL) cholesterol. Data indicate that dietary cholesterol has little effect on the plasma LDL:HDL ratio. Analysis of the available epidemiological and clinical data indicates that for the general population, dietary cholesterol makes no significant contribution to atherosclerosis and risk of cardiovascular disease. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

The relationship between dietary cholesterol and coronary heart disease (CHD) has been a topic of

intense research, and considerable debate, for a good part of the 20th century. From the 1913 animal studies of Anitschkow and Chalator [1] showing that feeding cholesterol to rabbits induced atherogenesis to the 1999 epidemiological surveys reported by Hu et al. [2] and Ascherio et al. [3] indicating that dietary cholesterol is unrelated to CHD risk, the dietary cholesterol-CHD risk relationship has gone from

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a hypothesis to a widely accepted belief to what many today consider to be an ineffective dietary restriction.

The concept that dietary cholesterol contributes to hypercholesterolemia and CHD risk has been a fundamental part of public health policy and dietary recommendations in the United States for over 30 years. In the 1970s the recommendation that cholesterol be restricted in the diets of the general population, and severely restricted in the diets of those with hypercholesterolemia, was based on three lines of evidence: (1) animal studies showing that dietary cholesterol induces hypercholesterolemia and atherosclerosis in some species; (2) epidemiological surveys reporting a positive relationship between dietary cholesterol and CHD incidence; and (3) clinical observations that feeding cholesterol increases plasma total cholesterol levels. Based on this evidence, a number of organizations recommended restricting dietary cholesterol levels for the population in an effort to reduced plasma cholesterol levels and CHD risk [4–8].

Over the last quarter century an extensive body of research on the relationship between dietary cholesterol and both blood cholesterol levels and CHD incidence has been published. These studies include large epidemiological surveys in populations followed for extended time periods as well as numerous feeding trials which investigated the effects of dietary cholesterol on plasma total and lipoprotein cholesterol levels and on whole body cholesterol and lipoprotein metabolism. This review summarizes the current state of research on the association between dietary cholesterol and atherosclerosis.

2. Animal studies

The plasma cholesterol response to dietary cholesterol is highly variable across and within animal species. While rabbits are highly susceptible to dietary cholesterol, rats and dogs exhibit little change in plasma total cholesterol even with high doses of dietary cholesterol. Non-human primates are highly variable in their responses to dietary cholesterol [9] and in many species it is only with extremely high doses of dietary cholesterol (0.5–2 mg/kcal or 1250–5000 mg/2500 kcal) that hypercholesterolemia and athero-

sclerosis can be induced. Another complication of animal studies is that most animal species have a significantly different plasma lipoprotein profile compared to humans. Whereas humans have low density lipoprotein (LDL) cholesterol as the predominant plasma lipoprotein, most animal models have high density lipoprotein (HDL) cholesterol as the major fraction. The species differences in the response to dietary cholesterol, the use of pharmacological doses of dietary cholesterol in many studies, and differences in the plasma lipoprotein profile make extrapolations from the results of animal feeding studies to human health recommendations difficult, if not impossible.

3. Epidemiological surveys

Historically, cross-cultural epidemiological surveys have been some of the strongest evidence that dietary cholesterol is associated with CHD incidence. Many epidemiological studies have reported a significant positive relationship between dietary cholesterol and both plasma total cholesterol levels and CHD incidence using simple regression analyses. For example, as shown in Fig. 1, data from the Seven Countries Study indicate a significant correlation between the population average cholesterol intake (mg/1000 kcal) and the 25 year mortality rate from CHD ($R^2 = 0.298$, $P = 0.029$) [10]. However, with today's understandings of the relationships between dietary factors and CHD risk, it is clear that two confound-

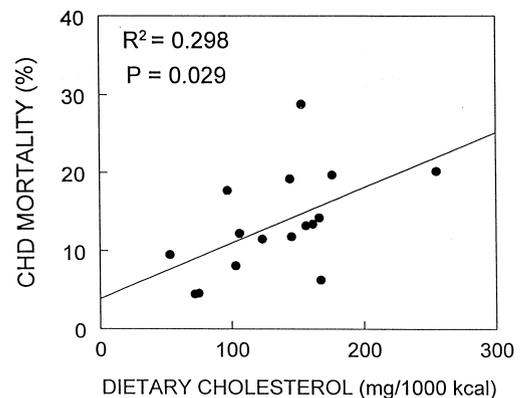


Fig. 1. Correlation of mean dietary cholesterol (mg/1000 kcal) and 25 year CHD mortality (%) in 12 763 men from the 16 cohorts of the Seven Countries Study [10].

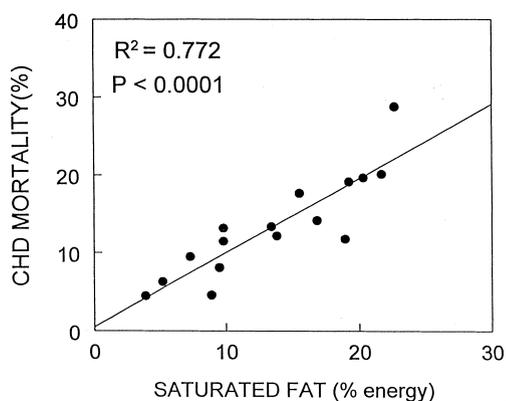


Fig. 2. Correlation of mean saturated fatty acid intake (% kcal) and 25 year CHD mortality (%) in 12 763 men from the 16 cohorts of the Seven Countries Study [10].

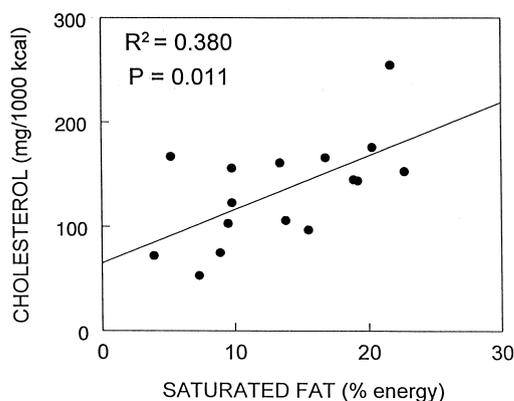


Fig. 3. Correlation of mean saturated fatty acid intake (% kcal) and mean dietary cholesterol (mg/1000 kcal) in 12 763 men from the 16 cohorts of the Seven Countries Study [10].

ing variables significantly impact on the interpretation of these epidemiological data. Cholesterol intake serves as a surrogate marker for two other dietary patterns associated with increased CHD risk; a high intake of saturated fat resulting in elevated plasma cholesterol levels, and a dietary pattern low in fruits, grains and vegetables resulting in lower intakes of B vitamins, antioxidants and dietary fiber.

A consistent finding of epidemiological studies of the relationships between dietary factors and CHD incidence is that the percent saturated fat calories in the diet are positively correlated with CHD incidence as shown in Fig. 2 for the Seven Countries Study ($R^2 = 0.772$, $P < 0.0001$) [10]. As shown in Fig. 3, these data also demonstrate that dietary saturated fat and cholesterol are related covariables ($R^2 = 0.380$, $P = 0.011$). As the data demonstrate, dietary cholesterol in a simple regression analysis is positively related to CHD incidence but, when multivariate analysis of the data accounts for the collinearity of dietary cholesterol and saturated fat, dietary cholesterol is no longer significantly related to CHD mortality rates ($P = 0.976$). Similar findings were re-

ported in 1988 by Hegsted and Ausman in an analysis of dietary data from the Twenty Countries Study [11]. These authors found that dietary cholesterol was significantly related to CHD incidence with simple correlation analysis but no longer statistically significant when multivariate analysis including saturated fat calories was used to analyze the data (Table 1).

In many of the more recent epidemiological surveys, investigators have noted that with simple correlations dietary cholesterol is sometimes correlated with CHD incidence but, upon inclusion of saturated fat and dietary fiber in the analyses, dietary cholesterol loses its significant relationship with CHD incidence [2,3,12,13]. It is clear that any evaluation of the epidemiological evidence for a relationship between dietary cholesterol and atherosclerosis accounts for the association between dietary cholesterol and saturated fat in the diet and that the data be evaluated using multivariate analysis to correct for confounding by the significant impact of dietary saturated fat.

Table 1
Diet and CHD in 20 countries: regression coefficients^a

Regression analysis	Cholesterol	Saturated fat	Polyunsaturated fat
Simple	3.75*	44.1*	-26.7*
Multiple	-1.90	61.1*	-31.8*

* $P < 0.05$.

^aData from Hegsted and Ausman [11].

4. Relationship between dietary cholesterol and CHD

In 1995, Ravnskov [14] published a review of 13 case-control studies carried out between 1968 and 1985 which measured dietary cholesterol intakes and CHD (Fig. 4) [15–23]. The mean cholesterol intake in CHD patients was 223 ± 11 mg/1000 kcal compared to controls with an average intake of

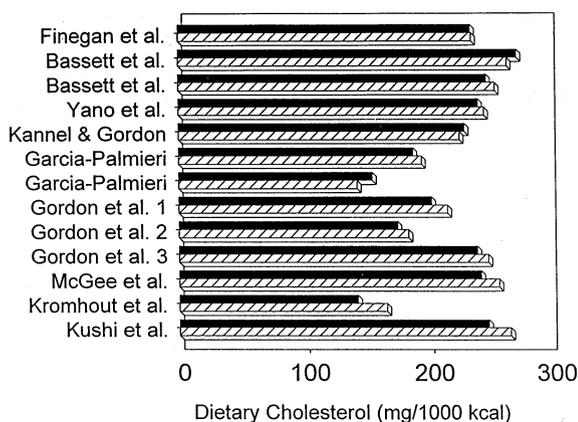


Fig. 4. Cholesterol intakes (mg/1000 kcal) of CHD cases and controls in 13 case-control studies [14]. Data from Kannel and Gordon [15], Garcia-Palmieri et al. [16], Gordon et al. [17], McGee et al. [18], Kromhout et al. [19], Kushi et al. [20], Bassett et al. [21], Finegan et al. [22], and Yano et al. [23].

216 ± 11 mg/1000 kcal ($P=0.021$). The mean difference between CHD cases and controls was 6.4 mg/1000 kcal equivalent to a difference in dietary cholesterol of 16 mg/day for someone on a 2500 kcal diet. Given that the CHD cases also had a higher intake of saturated fat calories than controls ($P=0.009$), it is not surprising that the cases had higher cholesterol intakes. Whether the increased CHD risk was due to the higher intake of saturated fat or to cholesterol cannot be decided from these data; however, it is difficult to propose a plausible biological explanation for an increased CHD risk with a 16 mg/day change in dietary cholesterol given that the daily metabolism of dietary and endogenously synthesized cholesterol in the body is over 1000 mg. Based on these data, Ravnskov [14] concluded that these case-control studies do not provide convincing evidence for a relationship between dietary cholesterol and CHD risk.

Epidemiological studies published in the last decade on the role of dietary factors in CHD risk have routinely employed multivariate analyses of the data to account for the effects of associated variables such as saturated fat and dietary fiber [24]. For example, Watts et al. [25] reported data from the St. Thomas Atherosclerosis Regression Study relating nutrient intake and progression of coronary artery disease in 50 males. In univariate linear regression analysis, progression of disease over 39 months was related to dietary energy ($P<0.001$), total fat ($P<0.001$), saturated fat ($P<0.001$) and cholesterol

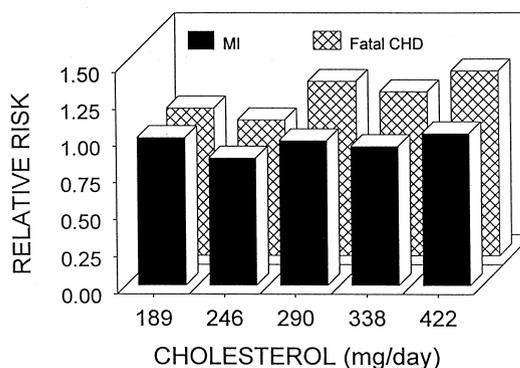


Fig. 5. Relative risk of myocardial infarction (MI) and of fatal CHD relative to mean dietary cholesterol intake quintile for 43 757 males in the Health Professionals Follow-Up Study [3]. There was no significant relationship between dietary cholesterol intakes and MI ($P=0.48$) or fatal CHD ($P=0.21$).

($P=0.06$) intakes. In multiple linear regression analysis, the association of progression with dietary cholesterol was no longer significant.

Esrey et al. [26] analyzed data from the Lipid Research Clinics Prevalence Follow-Up Study of 4546 men and women and reported that dietary cholesterol was not significantly related to CHD deaths in any age gender group. Ascherio et al. [3] reported a study of 43 757 males in the Health Professionals Follow-Up Study and found no relationship between quintile of cholesterol intake and either myocardial infarction or coronary deaths (Fig. 5). Dietary fiber intake had a significant effect on the relationships between dietary variables and CHD incidence, and inclusion of dietary fat and fiber in the multivariate analyses re-

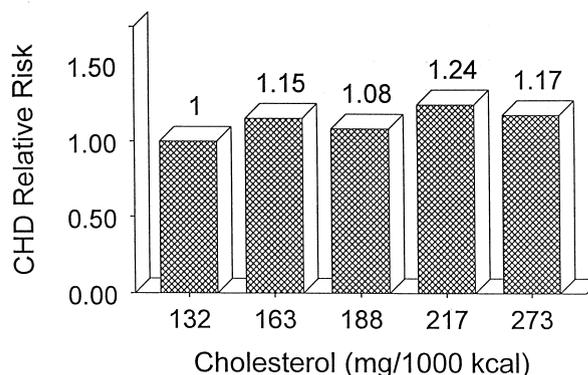


Fig. 6. Relative risk of CHD per quintile of dietary cholesterol intake for 80 082 women in the Nurses' Health Study [2]. There was no significant relationship between dietary cholesterol intakes and CHD ($P=0.24$).

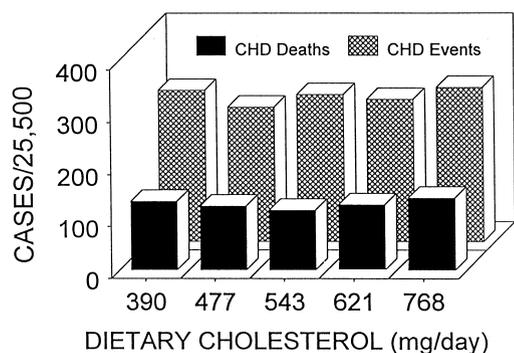


Fig. 7. Incidences of CHD events and CHD deaths for quintile of dietary cholesterol intakes in 21 930 men in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [12]. There was no significant relationship between dietary cholesterol intakes and CHD events ($P=0.81$) or CHD deaths ($P=0.77$).

sulted in a non-significant effect of dietary cholesterol. Hu et al. [2] reported data from 80 082 women in the Nurses' Health Study showing that dietary cholesterol was not related to CHD incidence (Fig. 6). As in the Health Professionals Study, relative risk for CHD did not differ for women in the quintiles of cholesterol intakes. Noted in this report was a significant relationship between dietary cholesterol and saturated fatty acids. Those in the lowest saturated fat intake had the lowest cholesterol intakes and vice versa.

Pietinen et al. [12] reported an analysis of diet-CHD relationships from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of 21 930 men. Consistent with findings from other epidemiological surveys, dietary cholesterol was not a significant contributor to CHD incidence, either events or deaths (Fig. 7). The intakes of cholesterol by this Finnish population were substantially higher than that of the various USA study groups yet the data indicate that even at these higher intakes (upper quintile 768 mg/day), dietary cholesterol was not related to CHD incidence. In a Greek case-control study, Tzonou et al. [27] reported no association between dietary cholesterol and relative risk for CHD in 329 CHD patients and 570 controls.

Two studies have reported a positive association between dietary cholesterol and atherosclerosis using simple regression analyses. Tell et al. [28] published data from the Atherosclerosis Risk in Communities (ARIC) Study of 13 148 men and women relating dietary variables and carotid artery wall thickness.

The authors reported that, after adjustment for age and energy intake, intake of animal fat, saturated fat, monounsaturated fat, and cholesterol were positively related to wall thickness, while vegetable fat and polyunsaturated fat intakes were negatively related. No analyses based on multiple linear regression analyses were reported. Mann et al. [29] reported the results from a study of 10 802 relatively healthy conscientious men and women (some 50% vegetarian) and found a significant relationship between tertiles of dietary cholesterol and ischemic heart disease mortality. These data were analyzed using univariate analyses and the interactive effects of saturated fat and dietary fiber on the dietary cholesterol relationship were not tested.

Other studies have investigated the relationships between dietary factors and CHD incidence, and while dietary cholesterol was included as a measured dietary variable in the study, the primary data were not reported for cholesterol; however, the text contains a statement that dietary cholesterol was not a significant factor (see for example [30,31]). Willett recently summarized the results from 20 prospective cohort studies of dietary factors in relation to risk of CHD and noted that dietary cholesterol was reported to be significantly associated with CHD in only two studies [24]; and in these two studies only simple regression analyses were reported.

5. Eggs and atherosclerosis

One-third of the cholesterol in the American diet

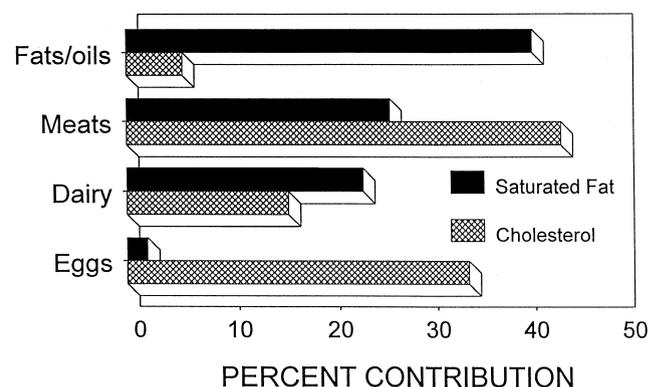


Fig. 8. Percent contribution of cholesterol and saturated fat from fats/oils, meats, dairy products and eggs in the US diet [32].

comes from eggs, a high-cholesterol, low-saturated fat food while two-thirds of the cholesterol come from other animal products which contribute both cholesterol and a high percentage of the saturated fat in the diet (Fig. 8) [32]. While the evidence for a relationship between total dietary cholesterol and CHD incidence are complicated by the colinearity of saturated fat with cholesterol in the diet, studies of the relationship between egg consumption and CHD specifically test whether dietary cholesterol is associated with CHD risk.

In 1982 Dawber et al. [33] reported no association between egg consumption and incidence of CHD in 912 participants in the Framingham Heart Study even with a 10-fold range of egg consumption between the lowest and highest tertile. Two other studies also reported no relationships between egg consumption and CHD incidence [34,35]. Data from the California Adventists Study indicated that CHD relative risk was 1.01 with a higher egg intake (≥ 3 per week) compared to the lowest intake (< 1 per week) [35]. Gramenzi et al. [34] reported data from a case-control study indicating that the CHD relative risk (RR) for women in the upper third of egg intake was 0.8 compared to those in the lower third.

Hu et al. [36] reported data from the Nurses' Health Study (NHS, $n = 80\,082$ followed for 14 years) and Health Professionals Follow-Up Study (HPFS, $n = 37\,851$ followed for 8 years) on the relationships between egg consumption and risk of CHD and stroke. The investigators classified egg consumption patterns into five groups: < 1 egg/week, 1 egg/week, 2–4 eggs/week, 5–6 eggs/week and ≥ 1 egg/day. The

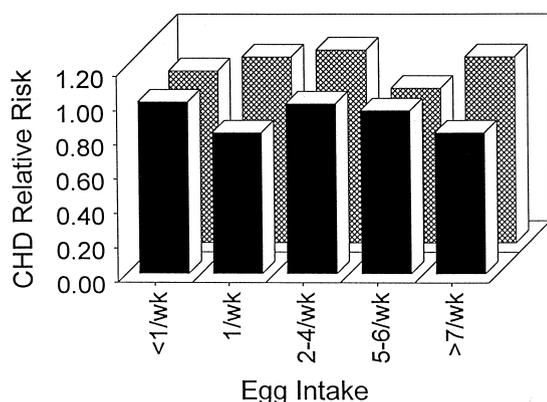


Fig. 9. Relative risk of CHD incidence in 37 851 males (Health Professionals Follow-Up Study) and 80 082 females (Nurses' Health Study) versus weekly egg consumption [36].

results were analyzed using a multivariate model including total energy, smoking, alcohol consumption, hypertension, parental history of CHD, body mass index, multivitamin use and vitamin E supplement use. As shown in Fig. 9, egg consumption, up to 1+ eggs per day, was unrelated to CHD risk in women (RR 0.82, 95% confidence interval (CI) 0.60–1.13, P for trend 0.95) and in men (RR 1.08, 95% CI 0.79–1.27, P for trend 0.75). Egg consumption was also unrelated to risk of either ischemic stroke (RR for 1+ eggs/day 0.81, 95% CI 0.46–1.42, P for trend 0.81) or hemorrhagic stroke (RR for 1+ eggs/day 1.07, 95% CI 0.56–2.03, P for trend 0.81).

The investigators determined that the background cholesterol intake did not change the findings. In the Nurses' Health Study 4.8% (3844) reported that they almost never ate eggs and 1.6% (1281) reported consuming two or more eggs a day. Comparison of these two extreme groups using multivariate analysis indicated that the relative risk for CHD was 0.76 (95% CI 0.43–1.35) in the high egg consuming group compared to those who never ate eggs [36].

In a subgroup analysis (stratified risk factors including hypercholesterolemia, diabetes, hypertension, smoking, alcohol use, body mass index, age, and intakes of saturated fat, polyunsaturated fat and carbohydrates) the authors reported that there was no evidence of a positive association of egg consumption and CHD in any subgroup except a suggestion of elevated risk among those with diabetes. The observation that egg consumption increased CHD risk in male and female diabetics in the study by Hu et al. [36] is in contrast to the report by Toeller et al. [13] from the EURODIAB IDDM Complications Study that dietary cholesterol was not significantly related to either plasma cholesterol levels or CHD incidence in 2868 subjects with type I diabetes. The interactions between eggs [36], dietary cholesterol and dietary fiber [13], type of diabetes, and CHD risk clearly needs further research to determine what factors are involved in increasing CHD risk.

Data from the Seven Countries Study and other epidemiological surveys reported positive correlations between total cholesterol intakes and CHD mortality rates across populations. Surprisingly, a similar analysis of egg consumption versus CHD mortality rates indicates that there is a negative relationship between per capita egg consumption and

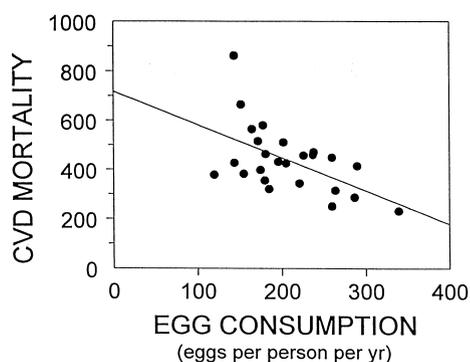


Fig. 10. Relationship between CVD mortality rates per 100 000 men aged 35–74 years [37] and per capita egg consumption in 24 industrialized countries (Annual Promotion and Marketing Survey No. 30, International Egg Commission, London, 1999).

CHD mortality rates per 100 000 men age 35–74 in 24 industrialized countries (Fig. 10). Similar results are obtained when the data are analyzed using female CHD mortality rates. The countries with the highest per capita egg consumptions are Japan, Mexico, Spain and France which have low CHD mortality rates [37].

The studies which have reported data on egg consumption and CHD rates uniformly indicate a null relationship and suggest that the previously observed positive relationship between total dietary cholesterol and CHD mortality rates is in large part explained by the association between dietary saturated fat calories and dietary cholesterol, and the low fiber intakes in diets high in animal products [2,3,13,36].

6. Independent effect of dietary cholesterol on CHD

Shekelle and Stamler [38] reported that in the Western Electric Study those individuals in the upper most quintile of cholesterol intakes had significantly increased relative risk for CHD even after adjustment for plasma cholesterol levels. The level of cholesterol intake in the fifth quintile averaged 1079 mg/day and was associated with an increased CHD incidence. In contrast, the fourth quintile, with an average cholesterol intake of 827 mg/day, was not significantly different than the bottom quintile. There are two aspects of this report which need to be considered. The first is the recognition that dietary factors can influence CHD risk through pathways other than changes in plasma cholesterol levels. The second

is that this extreme cholesterol intake in the top quintile suggests that the overall dietary pattern of these individuals was substantially more complicated than just high in cholesterol. This level of cholesterol intake suggests extreme intakes of animal products and, correspondingly, low intakes of grains, fruits and vegetables. Here again, dietary cholesterol serves as a surrogate marker for high intakes of saturated fat and animal protein as well as low intakes of grains, vegetables, and fruits in this subset. The unresolved question is whether the higher CHD incidence in this group was due to what was excessive in the diet or, perhaps, what was inadequate in the diet. With today's understanding of the role of dietary fiber, vegetable protein, antioxidants and B vitamins in CHD risk [39–41], it is clear that increased risk occurs not only from nutrient excesses but also from suboptimal intakes of specific nutrients. The potential importance of such confounding dietary variables, which could contribute to the higher CHD incidence in this quintile, was not evaluated by Stamler and colleagues and raises questions regarding the 'independent effect' hypothesis.

In contrast, studies reported by Connor and co-workers [42] indicate that different populations consuming diets with similar Cholesterol-Saturated Fat Index (CSI: $1.01 \times \text{g SFA} + 0.05 \times \text{mg cholesterol per 1000 kcal}$) values have different CHD incidence rates. While France and England have similar dietary CSI patterns, they differ almost 5-fold in CHD mortality rates. These investigators concluded that a high CSI value was not a contributor to CHD risk if the diet contained large amounts of fruits and vegetables and vegetable oils. Similarly, in the Ireland-Boston Study the CHD cases had a lower vegetable food score (-0.44 vs. 0.06) and a higher animal food score (0.24 vs. -0.04) than controls [20]. These data are consistent with the concept that the diet-heart disease relationship is a function of both what is in the diet, as well as what is missing from the diet and only through appropriate correction for confounding dietary factors can valid dietary associations with CHD be determined.

7. Clinical studies

It is not possible to have a direct clinical trial of

the effects of dietary cholesterol on atherosclerosis, and accordingly studies have investigated the effects of dietary cholesterol on plasma lipids and lipoproteins, and endogenous cholesterol and lipoprotein metabolism. The early metabolic ward studies consistently documented an increase in plasma total cholesterol levels with an increase in cholesterol intake and predictive equations were reported in 1965 by Keys [43] and Hegsted [44]. There have been a large number of cholesterol feeding studies carried out over the past 40 years and these studies have been analyzed in detail by numerous investigators [45–55]. The overall consensus is that dietary cholesterol does have a statistically significant, small effect on plasma cholesterol levels, and that the plasma cholesterol response to dietary cholesterol is highly variable, with about 75–80% of the population classified as hypo-responders and 15–20% as hyper-responders. Most analyses of the data indicate that the average plasma cholesterol response to a 100 mg/day change in dietary cholesterol is between 2.2 and 2.5 mg/dl [48,52,53]. Meta-analyses of the data indicate that the plasma cholesterol response to dietary cholesterol is independent of dietary fat type and amount, and unrelated to the baseline plasma cholesterol level [48,52,53]. There also is no evidence for gender differences in the plasma cholesterol response to a dietary cholesterol challenge [56].

The clinical data justifying dietary cholesterol restrictions are based on the early observations that dietary cholesterol raises plasma cholesterol which was the endpoint for determining dietary effects on CHD risk. The clear evidence that dietary cholesterol does in fact increase plasma cholesterol to a small degree (0.024 mg/dl per mg/day) would seem to conflict with the epidemiological evidence that dietary cholesterol is not associated with CHD risk. However, the effects of dietary cholesterol on plasma total cholesterol cannot provide a true estimate of its effects on CHD risk since changes can occur in both the atherogenic LDL cholesterol fraction as well as in the anti-atherogenic HDL cholesterol fraction. The meta-analysis of metabolic ward cholesterol feeding studies reported by Clarke et al. [52] indicates that dietary cholesterol increases total cholesterol levels by increasing both LDL and HDL cholesterol levels. A 100 mg/day increase in dietary cholesterol

increases the plasma LDL cholesterol by 1.9 mg/dl and HDL cholesterol by 0.4 mg/dl. Numerous cholesterol feeding studies have reported that dietary cholesterol has no effect on the LDL:HDL cholesterol ratio [57–62]. Thus, it is possible to increase total plasma cholesterol levels without a significant change in CHD risk provided that the LDL:HDL ratio remains constant. Addition of 100 mg/day cholesterol to the diet of a subject with a plasma cholesterol profile of 220 mg/dl total cholesterol, 150 mg/dl LDL cholesterol and 50 mg/dl HDL cholesterol (LDL:HDL ratio = 3.00) would be predicted [52] to increase plasma LDL by 1.9 mg/dl and HDL by 0.4 mg/dl, yet these increases would result in no significant change in the LDL:HDL ratio (3.01) and, theoretically, no change in CHD risk.

Three studies have found that dietary cholesterol has no effect on postprandial lipoproteins or on the efficacy of plasma to facilitate cholesterol efflux from cells. Reports by Ginsberg et al. [57,58], Clifton and Nestel [63] and Knopp et al. [59] indicate that dietary cholesterol has no negative effects on the pattern of postprandial lipoproteins and that there are no significant increases in any candidate atherogenic particles with either acute or long term dietary cholesterol feeding. Blanco-Molina et al. [64] reported that cholesterol feeding to humans increased plasma-induced cholesterol efflux from cells in culture. These data do not provide any evidence that dietary cholesterol induces production of atherogenic lipoprotein particles or inhibits reverse cholesterol transport

8. Summary and conclusions

Over the past two decades there have been numerous reports from clinical trials of dietary cholesterol feedings, epidemiological surveys and prospective studies, and meta-analyses of various collections of dietary lipid feeding trials showing that dietary cholesterol has a small, but significant effect on plasma cholesterol levels (0.022–0.027 mg/dl per mg dietary cholesterol) which has little meaning relative to CHD risk. The epidemiological data from large populations consistently show that dietary cholesterol has little effect on CHD incidence. There have been no studies validating the ‘independent effect’ of dietary

cholesterol on CHD risk and this observation can readily be accounted for due to confounding dietary covariables.

And yet the argument is made that there is a positive relationship between dietary cholesterol and plasma cholesterol, and that while the increase in CHD risk may be too small to determine in epidemiological surveys, any reduction in plasma cholesterol is desirable and adds to overall CHD risk reduction. The finding that dietary cholesterol is positively related to both LDL cholesterol and HDL cholesterol, with little change in the LDL:HDL ratio, provides a different interpretation of the data and suggests that the reason epidemiological surveys fail to detect a relationship between dietary cholesterol and CHD incidence is because there is no measurable change in risk. There is good evidence to indicate that not all increases in plasma total cholesterol levels are related to increased CHD risk and that changes in atherogenic and anti-atherogenic lipoprotein particles are the major determinant of changes in CHD risk.

The original rationale for a dietary cholesterol restriction was based on three observations: simple regression analysis of cross-cultural epidemiological data showing a positive relationship between cholesterol intake and CHD incidence; animal studies showing that, in some species, dietary cholesterol induced hypercholesterolemia and atherosclerotic lesions; and metabolic ward experiments demonstrating that high intakes of cholesterol increased plasma cholesterol levels. Thirty years ago these observations were the basis for a recommendation that dietary cholesterol be limited to less than 300 mg/day. In large part this recommendation was based on the 'precautionary principle' which suggests that when information about risk is uncertain, it is prudent to assume the worst. Today the dietary cholesterol restriction is widely accepted even though there are in fact limited data to support it, and considerable data accumulated over the last quarter century which contradict it. The recommendation persists in large part because it is an established part of public health policy. As noted by Dr. Walter Willett [65] regarding public confusion with ever changing diet and health issues: 'One of the problems is that strong recommendations have often been made on very weak data. It may have been the best guess at the moment.

But often the recommendations are repeated so many times that people forget they were rough guesses in the first place and come to think they are hard facts.' Public health recommendations can become dogma without the necessary scientific evidence, and eventually become impervious to argument and re-evaluation. The dietary cholesterol recommendation is so widely accepted that it is now in the situation of 'reverse onus' where it is no longer necessary for those making the recommendation to prove its validity but rather it is up to those who question the restriction to prove it is not scientifically justified.

In a discussion regarding community interventions to postpone CHD, Shaper and Marr [66] noted over 20 years ago that there was considerable confusion regarding dietary intervention strategies and that 'This confusion is aggravated by the production of diet sheets and cookery books designed to provide *low-cholesterol* rather than *cholesterol-lowering* diets. The emphasis on the role of dietary cholesterol tends to diminish the impact of more important recommendations about the types of fat in the diet.'

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