

## Nuts and coronary heart disease: an epidemiological perspective

John H. Kelly Jr and Joan Sabaté\*

Department of Nutrition, School of Public Health, Loma Linda University, Loma Linda, CA 92350, USA

The epidemiological evidence for the cardio-protective effect of nut consumption is presented and reviewed. Four large prospective epidemiological studies of primary prevention of coronary heart disease are reviewed and discussed (Adventist Health Study, Iowa Women's Health Study, Nurses' Health Study and the Physicians' Health Study). Other studies of nuts and coronary heart disease risk are addressed. The combined evidence for a cardio-protective effect from nut consumption is summarized and presented graphically. The risk of coronary heart disease is 37% lower for those consuming nuts more than four times per week compared to those who never or seldom consume nuts, with an average reduction of 8.3% for each weekly serving of nuts. The evidence for a causal relationship between nut consumption and reduced risk of coronary heart disease is outlined using Hill's criteria for causality and is found to support a causal cardio-protective relationship.

**Nuts: Cardiovascular: Coronary heart disease: Diabetes: Cohort studies: Causality: Hill's criteria**

Nuts have constituted a part of mankind's diet since pre-agricultural times (Eaton & Konner, 1985), providing a complex food rich in macronutrients and micronutrients and fibre, as well as other bioactive phytonutrients yet to be discovered. While the amount of nuts in the human diet in the distant past is unknown, recent data indicates nut consumption was declining in the 1980s, although nut consumption in countries following a more Mediterranean diet is twice that of the American diet (Dreher *et al.* 1996).

This decrease in nut consumption relative to other food groups is likely related to commonly held beliefs that high-fat foods should be used sparingly as a result of public health messages to reduce fat intake. This was due to the implication of fat as a risk factor for chronic diseases such as coronary heart disease and some cancers, the leading causes of death in Western countries and, increasingly, in the world. Although total fat intake has an important effect, it is now well established that the fatty acid composition rather than the total amount of fat consumed is the predictor of serum cholesterol. Nuts are approximately 60% fat by weight but, unlike animal foods that are a primary source of saturated fat and offer little fibre, are comprised mainly of unsaturated and polyunsaturated fatty acids and are a good source of fibre. This difference has focused attention on the investigation of the effects of nut consumption in lessening coronary disease risk and prompted the hypothesis on how a diet that includes nuts may favourably influence plasma lipids (Sabaté & Fraser, 1994).

This paper reviews and summarizes the epidemiological evidence of nut consumption in the primary and secondary prevention of coronary heart disease (CHD). The epidemiological data relating nuts and CHD risk has been reviewed previously elsewhere (Sabaté, 1999; Sabaté *et al.* 2001) and by others (Hu & Stampfer, 1999; Kris-Etherton *et al.* 2001). In

this paper we also address each of Hill's criteria for causality in examining the link between nuts and CHD risk.

### Studies of nut consumption and primary prevention of coronary heart disease

Since nuts were first found to be associated with reduced risk of heart disease in the Adventist Health Study over a decade ago, the majority of the epidemiological studies that looked at this relation have reported similar findings. Four large prospective epidemiological studies with significant findings are reviewed and their results discussed below.

#### *The Adventist Health Study*

The Adventist Health Study (AHS) was the first to generate interest in nuts and reduced risk of coronary heart disease (CHD). This prospective study of 31 208 California Seventh-day Adventists (Fraser *et al.* 1992) provided an opportunity to investigate the relationship between certain foods and chronic diseases. The AHS cohort is unique in its homogeneity in that the Adventist population is well-educated and highly interested in diet and health. There is almost no prevalence of smoking and little use of alcohol in the cohort, thus eliminating these factors as potential confounders. Two-thirds of the cohort is female. Half of the cohort consumes a vegetarian diet, providing a wide range of dietary intakes and frequency of nut consumption. Twenty-four percent of the subjects consumed nuts more than four times per week. This makes the cohort highly suitable for studying dietary relationships to coronary heart disease.

A food frequency questionnaire enquired about 65 food items, one of which was the use of nuts. Approximately 27 000 individuals ranging from 25 to 101 years of age had

\* Corresponding author: Joan Sabaté, fax +909 558-4095, email jsabate@llu.edu

dietary and lifestyle habits recorded. Annual questionnaires and medical report findings followed CHD data for six years (1977–82). Independent relationships between several foods at baseline and the end points of nonfatal myocardial infarction or death from CHD were considered. Questions for nut consumption included categories from ‘never consume’ to ‘more than once per day’. Data were stratified according to age, sex, smoking, exercise, relative weight and hypertension to control for confounding.

The frequency of nut consumption was inversely related to the risk of having a non-fatal myocardial infarction (MI) or dying of coronary heart disease (CHD). Nuts had the strongest inverse relationship of all foods evaluated in this cohort. After multivariate analysis, the strong inverse relationship between nut consumption and risk remained statistically significant, suggesting that these findings were unlikely to be the result of chance alone. Those who ate nuts 1–4 times per week had a 26% reduction in risk of non-fatal MI and a 27% reduction in risk of dying from CHD compared to those consuming nuts less than once per week, whereas those eating nuts five or more times per week showed a 48% reduction in risk of MI ( $P$  for trend  $<0.01$ ) and a 38% reduction in risk of death from CHD ( $P$  for trend  $<0.05$ ) (Fraser *et al.* 1992) (Fig. 1).

The protective effect of nuts was seen in both vegetarians and non-vegetarians, although their beneficial effect was somewhat attenuated in those who consumed meat (Sabaté, 1999). This attenuation was more evident in those who consumed a more moderate amount of nuts, indicating a higher intake may be required to realize the cardio-protective effect of nuts in non-vegetarians. In this cohort, nut consumption five or more times per week seems to confer protection against CHD, even in the oldest subjects (those over 84 years of age) (Fraser & Shavlik, 1997).

Subsequent publications from the Adventist Health Study assessed the lifetime risk of developing CHD and computed age at first coronary event. Lifetime risk of CHD development was reduced by 12% in the group eating nuts five or more times per week, and men who did develop the disease did so 5.6 years later than men who ate nuts infrequently (Fraser *et al.* 1995). These results suggest that high nut consumption not only decreases the risk of developing CHD,

but also postpones the development by several years in those who do acquire the disease.

#### The Iowa Women's Health Study

The Iowa Women's Health Study (Kushi *et al.* 1996) is a prospective study of ~34 000 postmenopausal women aged 55 to 69 years at enrolment. Intake was assessed for 127 foods including nuts using a food frequency questionnaire, as well as lifestyle factors relevant to coronary heart disease (CHD). Established risk factors for CHD, such as hypertension, body mass index and smoking, were higher in this cohort of women from Iowa than in the AHS cohort of California Seventh-day Adventists. Nut consumption in this population was also considerably lower than in the AHS cohort: 41% never ate nuts, 35% ate them one to three times per month, 15% ate them once per week, and only 9% ate nuts two or more times per week.

Despite the sizeable difference in nut consumption from women in the AHS, the results after 7 years of follow-up among 19 411 women not using vitamin supplements were similar. Those in the highest quartile of nut consumption had a 40% reduction in risk of fatal CHD compared to the lowest quartile that seldom or never ate nuts (RR 0.60, 95% CI, 0.36–1.01,  $P$  for trend 0.016) (Kushi *et al.* 1996).

Results after 12 years of follow-up based on the baseline questionnaire were attenuated. This is not unexpected in studies of chronic disease due to the effects of ageing and ongoing changes in dietary patterns. In the multivariate analysis adjusting for numerous risk factors (age, total energy intake, body mass index, waist-to-hip ratio, smoking, hypertension, diabetes, contraceptive use, oestrogen-replacement therapy, physical activity, alcohol use, marital status and education), an inverse relationship between nut consumption and risk of death from CHD was still present. The highest category of nut consumption ( $>1$  week) had a risk reduction of 19% compared to those who ate nuts less than once per month, although this association did not attain statistical significance (RR 0.81, 95% CI 0.60–1.11,  $P$  for trend 0.30) (Ellsworth *et al.* 2001). Interestingly, there was also a weak inverse relationship between all-cause mortality and nut consumption.

Results after 15 years of follow-up are presented in another article of this supplement (Blomhoff *et al.* 2006). For that analysis on postmenopausal women without heart disease or diabetes at baseline, the combined frequency of consumption of nuts plus peanut butter shows strong and consistent reductions in risk of CHD death. After adjusting for recognized CHD risk and dietary factors, women consuming nuts/peanut butter one to four times per week and five or more times per week had, respectively, an 18 and 29% risk reduction of CHD deaths. Substantial reductions in total mortality are also observed on those frequently consuming nuts and peanut butter (Blomhoff *et al.* 2006).

#### The Nurses' Health Study – coronary heart disease

The Nurses' Health Study (NHS) (Hu *et al.* 1998) also investigated the relationship between nut consumption and coronary heart disease (CHD). This prospective study of female nurses aged 30–55 years from several states is the largest epidemiological study to examine this association. The results shown

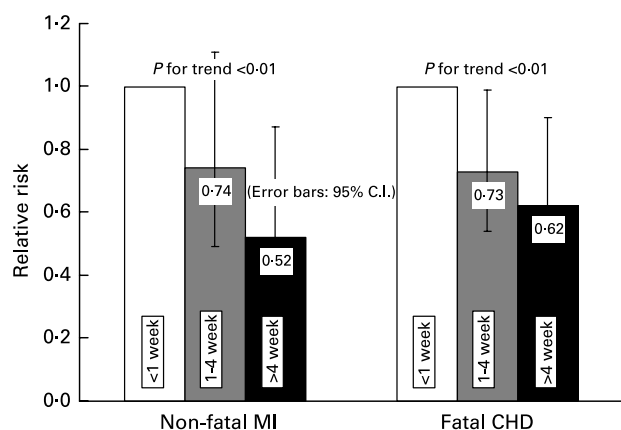


Fig. 1. Risk of non-fatal myocardial infarction (MI) and fatal coronary heart disease (CHD) by frequency of nut consumption, Adventist Health Study.

here for 86 016 middle-aged women confirm earlier published studies including older men and women, demonstrating that the cardio-protective effect of nuts spans gender and age.

Beginning in 1980, detailed information on medical history and lifestyle was collected and questionnaires were completed every 2 years during the 14 years of follow-up (1980–94). The 61-food item dietary questionnaire assessed frequency of intake of nuts and peanut butter. Data were also obtained for fatal and non-fatal myocardial infarction (MI) events during follow-up.

After adjusting for major recognized CHD risk factors (age, BMI, smoking, hypertension, diabetes, hypercholesterolemia, hormone use, parental history of MI, vitamin use, alcohol, aspirin, vigorous exercise and total energy intake), there was a 39% reduction of fatal CHD (RR 0.61, 95% CI 0.35–1.05,  $P$  for trend 0.007), a 32% reduction of non-fatal MI (RR 0.68, 95% CI 0.47–1.0,  $P$  for trend 0.04) and a 35% reduction in total CHD (RR 0.65, 95% CI 0.47–0.89,  $P$  for trend <0.001) for nurses who consumed nuts five or more times per week compared to those eating nuts less than once per month. (Fig. 2) The relative risk was not significantly changed by adjustment for potential confounding dietary factors such as trans- and saturated fats, fruit and vegetable intake, etc., indicating nuts were independently associated with a reduced risk of heart disease. When the analysis was restricted to non-smokers who consumed little alcohol, the association was even stronger with a 52% reduction in CHD risk (RR 0.48, 95% CI 0.27–0.84,  $P$  for trend 0.008).

#### The Nurses' Health Study – type-2 diabetes

In addition to cardiac outcomes, the NHS also followed the incidence of type-2 diabetes in this population of nurses (Jiang *et al.* 2002). Diabetes is a major risk factor for CHD since diabetics have a two- to four-fold increased risk of developing CHD (Haffner *et al.* 1998).

A total of 3206 new cases of type-2 diabetes were documented in 16 years of follow up (1980–19). Nut consumption was inversely associated with risk of type-2 diabetes after multivariate adjustment for traditional risk factors (age, BMI, family history of diabetes, physical activity, smoking, alcohol use, and total energy intake). The relative risks across

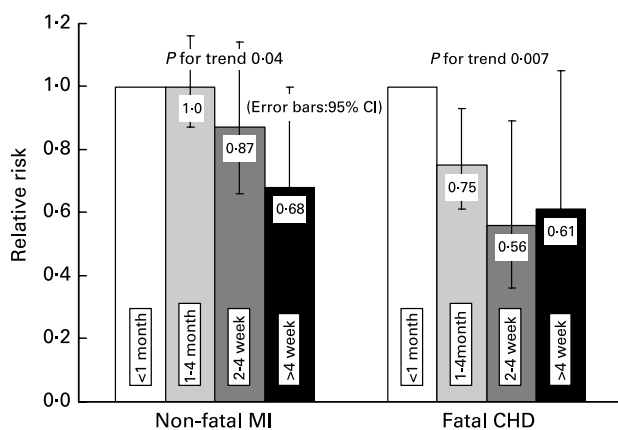


Fig. 2. Risk of non-fatal myocardial infarction (MI) and fatal coronary heart disease (CHD) by frequency of nut consumption, Nurses' Health Study.

categories of nut consumption (never/almost never, <once/week, 1–4 times/week, and >4 times/week) for a 1 oz. serving were 1.0, 0.92 (95% CI 0.85–1.00), 0.84 (0.95% CI 0.76–0.93), and 0.73 (95% CI 0.60–0.89,  $P$  for trend <0.001).

Further adjustment for intakes of dietary fats, cereal fibre, and other dietary factors did not appreciably change the results. The inverse association was also found after stratification by levels of BMI, smoking, alcohol use and other known diabetes risk factors. Consumption of peanut butter was also inversely associated with type-2 diabetes with a multivariate-adjusted relative risk of 0.79 (95% CI 0.68–0.91,  $P$  for trend <0.001) in women consuming peanut butter more than four times a week (equivalent to  $\geq 15$  oz. of peanuts per week) compared with those who never or almost never ate peanut butter. These findings show an increasing protective effect with increasing consumption, indicating that higher nut and peanut butter consumption lowers the risk of type-2 diabetes in women. This, in turn, lowers their risk of developing CHD.

#### The Physicians' Health Study

The Physician's Health Study (PHS) (The Steering Committee of the Physicians' Health Research Group, 1988) findings are consistent with the other studies, but weaker associations were found between nut consumption and coronary heart disease (CHD) (Albert *et al.* 2002). This prospective study of 22 071 physicians between 40 and 84 years of age in 1982 with no history of myocardial infarction, stroke, transient ischaemic attacks or cancer randomly assigned participants to receive aspirin, beta carotene, both active drugs or both placebos. The PHS cohort represents a well-educated and health conscious group of male professionals.

The relationship between nut consumption and end points of fatal and non-fatal myocardial infarction and death from CHD were evaluated. Multivariate models were used to control for confounders including previous CHD, body mass index (BMI), smoking, diabetes, hypertension, hypercholesterolemia, alcohol consumption, vigorous exercise, vitamin E and C and multivitamin use. In 17 years of follow up, frequency of nut consumption was inversely associated with death from CHD only for the highest intake category (more than once per week). Those consuming nuts more than once a week had a 33% reduction in risk of CHD death, although there was a non-significant trend (RR 0.77, 95% CI 0.59–1.0,  $P$  for trend 0.06) (Albert *et al.* 2002) (Fig. 3). Frequency of nut consumption was also inversely associated with risk of sudden cardiac death, but not of non-fatal myocardial infarction. After multivariate adjustment for confounding factors, the cardio-protective effect of nuts was strengthened for sudden cardiac death. Those who consumed nuts 1–3 times per week had a 20% reduction in risk of sudden cardiac death, those consuming nuts once per week had a 40% reduction, and those consuming nuts more than once a week had a 47% reduction in risk of sudden cardiac death ( $P$  for trend 0.01) (Albert *et al.* 2002) (Fig. 3).

A possible explanation for the weaker cardio-protective effects of nuts in the PHS and the disparate findings with respect to non-fatal myocardial infarction is the difference in the amount of nuts consumed. Twenty-four percent of the subjects in the AHS consumed nuts more than four times per

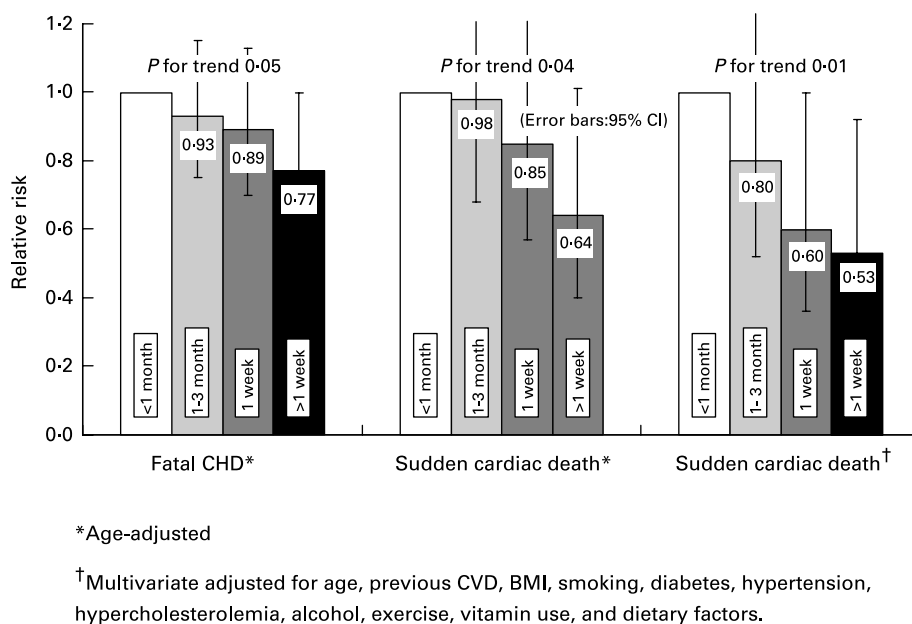


Fig. 3. Risk of fatal coronary heart disease (CHD) and sudden cardiac death by frequency of nut consumption, Physicians' Health Study.

week while only 6.3% of the physicians in the PHS consumed nuts at that level. It is likely that the cardio-protective effect of nuts is not as strong at the lower level of consumption found in the PHS cohort. It may also be that the cardio-protective effect is lower in non-vegetarians. The protective effect of nut consumption was weaker in the AHS among non-vegetarians and it is likely that their protective effects were less prominent in the largely non-vegetarian PHS cohort. Furthermore, collapsing the upper categories of consumption into a single category representing >1 week obliterated any effect gradient above >1 week. It is likely that an effect gradient exists that cannot be seen in this representation of the data.

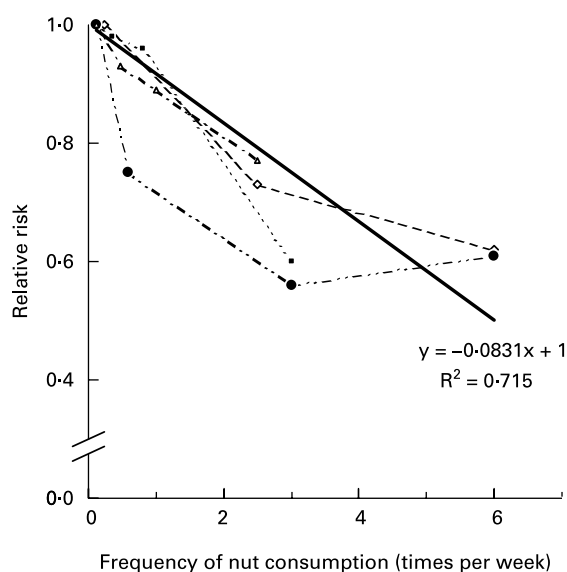
#### Summary of epidemiological findings on primary prevention

The findings from these four epidemiological studies show a consistent and remarkable cardio-protective effect associated with increased nut consumption. These effects are evident in all studies across a wide range of nut intakes and across subpopulations of males and females, differing ages, geographical locations and occupations. Also, the beneficial effect of nut consumption is similar for different clinical outcomes: non-fatal myocardial infarction, fatal CHD and sudden cardiac death.

Fig. 4 depicts a graphic and qualitative summary of data from the four prospective cohort studies reviewed above of nut consumption and primary prevention of CHD. Using the median of each category as the frequency of nut consumption associated with the relative risk for each category, there is a clear dose-response gradient in each study. The regression line (bold solid line in Fig. 4) represents the least squares best linear fit of the data from the four studies. The  $R^2$  of 0.715 indicates that approximately 70% of the variance in the relative risk among these studies is explained by a linear relationship between relative risk and frequency of nut consumption. The negative slope of the regression line indicates

risk is lower with increasing frequency of nut consumption. The slope of  $-0.0831$  suggests that there is an average reduction in the risk of CHD death of 8.3% for each unit increase in weekly frequency of nut consumption.

The highest nut consumption frequency values were collapsed into a single category in two of the studies (>1 per week in the IWHS and PHS), thus obliterating any gradient of effect for nut consumption higher than the collapsed classification. It is likely a gradient of effect exists above this level of consumption in those studies, as it does in the studies that



Solid bold line is the least squares best-fit linear regression of all four studies similarly adjusted for multiple risk factors.

Fig. 4. Risk of CHD death by frequency of nut consumption from four prospective epidemiological studies.  $\circ$ —, AHS;  $\blacksquare$ —, IWHS;  $\bullet$ —, NHS;  $\triangle$ —, PHS.

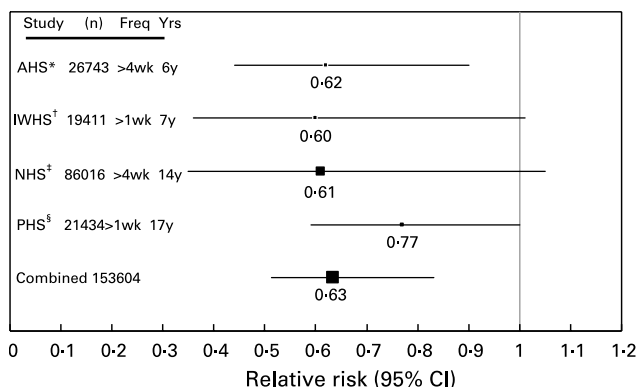


did not collapse the data. A gradient is suggested, but not proven, by the fact the relative risk is lower for the collapsed categories than for the same consumption in non-collapsed data, and the fact that the *P* for trend is very small for all of these studies.

The similarly adjusted findings from these four prospective cohort studies are pictured in Fig. 5 and provide unequivocal evidence of a clinically and statistically significant cardio-protective effect from nut consumption. The average risk reduction for CHD death in these four epidemiological studies of nut consumption and CHD is 37% (RR 0.63, 95% CI 0.51–0.83). Remarkable as these findings may be, residual confounding cannot be completely excluded on the basis of epidemiological studies alone, unlike randomized controlled trials that can approach causality.

### Nut consumption and secondary prevention of coronary heart disease

The Cholesterol and Recurrent Events Study (CARE) study (Brown *et al.* 1999) examined the cardio-protective effect of nuts in a population that had already experienced a non-fatal myocardial infarction. This study evaluated post-myocardial infarction outcomes in 3575 hypercholesterolemic men and women aged 21–75 years for an average of 4.2 years of follow-up. Those consuming more than one serving of nuts per week had a 25% lower risk of total CHD compared with those who rarely ate nuts or consumed less than one serving per month (RR 0.75, 95% CI 0.49–1.15, *P* for trend 0.03). This 25% reduction was present after adjustment for age, smoking and other established CHD risk factors. Adjustment for saturated fat, fibre, fruits and vegetables, minerals, and antioxidant vitamins did not significantly attenuate the cardio-protective effect. Thus, results of this study indicate that frequent nut consumption may also prevent recurrent CHD events.



\* Adventist Health Study (Fraser *et al.*, 1992)

† Iowa Women's Health Study (Kushi *et al.*, 1996)

‡ Nurses Health Study (Hu *et al.*, 1998)

§ Physicians Health Study (Albert *et al.*, 2002)

Relative risk and 95% confidence intervals derived from the comparison of incidence rates between the highest and lowest frequency of nut consumption and similarly adjusted for multiple risk factors. Size of marker represents number of subjects.

Fig. 5. Prospective cohort studies of nut consumption and coronary heart disease.

### Other epidemiological studies of coronary heart disease and risk factors

Evidence of a cardio-protective effect of nuts was found in a health conscious cohort of 10 800 men and women from England and Wales aged 16–79 whose diet resembled, in nutrient content, current dietary recommendations (Mann *et al.* 1997). After an average of 13.3 years of follow up, the death rate ratio (DRR) for ischaemic heart disease was lower in those consuming nuts more than four times per week compared to those eating nuts less than once per week (DRR 87, 95% CI 45–168). The authors conclude that 'with the possible exception of nuts, there was little evidence for an important role' for cardio-protective foods in this cohort. However, they go on to say that it is unclear whether this is due to 'inadequacies of the instrument' or whether 'protective foods and nutrients play a less important role' in groups who have adopted a healthy plant-based diet (Mann *et al.* 1997).

A cross-sectional study carried out in France (Lavedrine *et al.* 1999) found that the consumption of walnuts and walnut oil related to blood lipids in a population that typically consumes walnuts as part of their standard diet. Approximately 800 men and women between the ages of 18 and 65 years reported nut consumption using food frequency and dietary recall methods, and had blood specimens drawn. After controlling for gender, body mass index, dietary animal fat and alcohol, modest but significant increases in serum high-density lipoprotein (HDL) cholesterol (0.053 g/L, 95% CI 0.022–0.084) and apoprotein A1 (0.057 g/L, 95% CI 0.002–0.112) were observed among frequent walnut consumers (use walnut oil every day and eat walnuts more than twice per week) compared to non-consumers. No changes were found for low-density lipoprotein (LDL) cholesterol or triglycerides serum levels.

### Certainty of the causal link between nuts and coronary heart disease

The relationship between nut consumption and CHD is remarkable in how well it fulfils the generally accepted criteria for causation. In 1965, Sir Austin Bradford Hill enumerated nine widely accepted criteria (Hill, 1965) for establishing causality and brought order and reason to the logical process of determining causation. Hill's criteria are: temporality of events, strength of the association, dose-response gradient, consistency of results, plausible explanation, consideration of alternate explanations, experimental evidence, specificity and coherence. Chronic diseases are recognized as being multi-factorial in their causes, and coronary heart disease, more so than infectious disease, is undoubtedly the result of a multiplicity of agents or causes. Nonetheless, most of Hill's criteria are applicable in evaluating causality of chronic diseases, including CHD. Each of Hill's nine criteria is reviewed briefly below and examined to determine the cause and effect relationship between nut consumption and CHD:

- (1) Temporality requires that causes must precede effects in time. It is generally agreed that an event that occurs after another event cannot be the cause of the former event. All of the epidemiological studies of nut consumption and CHD were prospective, meaning that they examined associations between nut consumption that preceded

the incidence of new cases of coronary heart disease. A higher frequency of nut consumption was, in turn, followed by a lower incidence of coronary heart disease in each study.

- (2) The strength of the relationship between a hypothesized cause and its effect is an important criterion of causation. It is generally agreed that a stronger association is more likely to be present for a causative factor than is a weak association. Nonetheless, causative factors of multi-factorial disease may result in little difference in incidence. In the studies reviewed, the relative risk of death from CHD ranges from 0.60 to 0.77 for those consuming nuts frequently compared to those consuming them infrequently (Fig. 5). This represents a 23–40% reduction in the incidence of CHD from simply eating nuts. In nutritional epidemiology this is one of the strongest relations ever found between a single food and a chronic disease such as CHD.
- (3) The presence of a dose-response gradient is considered highly indicative of causation. A dose-response is present when increasing amounts of the causative factor are associated with stronger effects in a monotonic relationship. Higher frequency of nut intake is associated with decreased risk of CHD in each of these studies (Fig. 4). The *P*-value for trend, a statistical measure of dose-response, is significant for most analyses in these studies. There is a very clear dose-response relationship between nut consumption and cardio-protection. Furthermore, a dose-response relationship was found between nut consumption and serum cholesterol, a major CHD risk factor, in two randomized feeding trials specifically designed to test this criterion (Jenkins *et al.* 2002; Sabaté *et al.* 2003).
- (4) Consistency of findings is an important criterion. Epidemiological studies often exhibit mixed findings due to a variety of biases and confounders. The consistency of the findings in these studies of nut consumption and risk of CHD is remarkable. Epidemiological associations between many foods and risk of some chronic diseases demonstrate mixed results (World Cancer Research Fund/American Institute for Cancer Research, 1997), some studies having an RR < 1.0 and some > 1.0. On the contrary, epidemiological studies of nut and CHD without exception have found the RR for CHD to be less than 1.0 (Fig. 5).
- (5) Plausibility is also an important criterion for causation. The existence of a plausible explanation for the observed effect strengthens the argument for causation. On the other hand, the absence of an explanation cannot exclude causation since our knowledge is incomplete. A cardio-protective effect for nuts is biologically plausible. The improvement of serum lipids is a well-substantiated mechanism by which nut consumption reduces the risk of CHD (Sabaté *et al.* 2001). While nuts have a higher fat density than many foods, their fat is mainly unsaturated with a high ratio of unsaturated to saturated fats. Some also contain relevant amounts of omega-3 fats. These characteristics are accompanied by a higher fibre content than many foods. Beyond their fat and fibre content, nuts contain many other nutrients and constituents such as arginine-rich proteins, tocopherol, magnesium, copper and phytochemicals,

with potential cardio-protective effects (Sabaté & Fraser, 1994; Kris-Etherton *et al.* 1999).

- (6) Consideration of alternative explanations is a weaker criterion for multi-factorial diseases and one difficult to evaluate with epidemiological studies alone since the possibility of confounding due to chance associations cannot be excluded. Recognized alternative explanations have been excluded in the epidemiological studies by adjusting for all known risk factors.
- (7) Experimental evidence is one of the most important criteria of causation but is, by definition, not part of the epidemiological evidence. It can be noted, however, that multiple randomized feeding trials have been carried out on CHD risk factors using a variety of nuts and these experimental studies demonstrate a cardio-protective effect for nut consumption (Sabaté *et al.* 2001; Jenkins *et al.* 2002; Sabaté *et al.* 2003; Ros *et al.* 2004)
- (8) Specificity is the characteristic of a singular effect or relationship existing between two variables. This is particularly applicable to infectious disease, but is one of the weaker and less important criteria for multi-factorial diseases because multiple causes of chronic disease are quite common. It can be noted that nut consumption is not specific for cardio-protection, nor is reduced risk of CHD specific for nut consumption.
- (9) Coherence is the characteristic of agreement among all or most of the determining considerations. This is well demonstrated in the relationship between nut consumption and CHD risk. The plausible, consistent, strong, dose-response gradient for nut consumption and reduced incidence of CHD is highly coherent and rational.

## Conclusion

The epidemiological evidence could hardly be stronger in identifying a cardio-protective effect for nut consumption. Prospective epidemiological studies demonstrate amazing consistency of findings. While epidemiological studies cannot prove causation, Hill's criteria are fulfilled and dietary intervention trials have found reduced CHD risk factors with increased nut consumption.

Collectively, the epidemiological data indicates nuts may be one of the most cardio-protective whole foods commonly eaten. Coronary heart disease remains the leading cause of death worldwide. Increased frequency of nut consumption can substantially decrease CHD mortality. The average reduction in risk of CHD death is 8.3% for each serving of nuts consumed weekly (~30 g). Simply eating more nuts could save many lives.

Much research is needed to elucidate the specific mechanisms for this protective effect, which presents a fruitful field for future study. Meanwhile, nutritionists can encourage nut consumption, especially in those individuals with elevated risk of coronary heart disease.

## References

- Albert CM, Gaziano JM, Willett WC & Manson JE (2002) Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. *Arch Intern Med* **162**, 1382–1387.

- Blomhoff R, Carlsen MH, Andersen LF & Jacobs DR (2006) Health benefits of nuts: Potential role of antioxidants. *Br J Nutr* **96**, Suppl. 2, S52–S60.
- Brown L, Rosner B, Willett W & Sacks F (1999) Nut Consumption and risk of recurrent coronary heart disease. *FASEB J* **13**, A538.
- Dreher ML, Maher CV & Kearney P (1996) The traditional and emerging role of nuts in healthful diets. *Nutr Rev* **54**, 241–245.
- Eaton SB & Konner M (1985) Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med* **312**, 283–289.
- Ellsworth JL, Kushi LH & Folsom AR (2001) Frequent nut intake and risk of death from coronary heart disease and all causes in postmenopausal women: the Iowa Women's Health Study. *Nutr Metab Cardiovasc Dis* **11**, 372–377.
- Fraser GE, Lindsted KD & Beeson WL (1995) Effect of risk factor values on lifetime risk of and age at first coronary event. The Adventist Health Study. *Am J Epidemiol* **142**, 746–758.
- Fraser GE, Sabaté J, Beeson WL & Strahan TM (1992) A possible protective effect of nut consumption on risk of coronary heart disease. The Adventist Health Study. *Arch Intern Med* **152**, 1416–1424.
- Fraser GE & Shavlik DJ (1997) Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study. *Arch Intern Med* **157**, 2249–2258.
- Haffner SM, Lehto S, Ronnema T, Pyorala K & Laakso M (1998) Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* **339**, 229–234.
- Hill AB (1965) The Environment and Disease: Association or Causation? *Proc R Soc Med* **58**, 295–300.
- Hu FB & Stampfer MJ (1999) Nut consumption and risk of coronary heart disease: a review of epidemiologic evidence. *Curr Atheroscler Rep* **1**, 204–209.
- Hu FB, Stampfer MJ, Manson JE, Rimm EB, Colditz GA, Rosner BA, Speizer FE, Hennekens CH & Willett WC (1998) Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. *BMJ* **317**, 1341–1345.
- Jenkins DJ, Kendall CW, Marchie A, Parker TL, Connelly PW, Qian W, Haight JS, Faulkner D, Vidgen E, Lapsley KG & Spiller GA (2002) Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. *Circulation* **106**, 1327–1332.
- Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC & Hu FB (2002) Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA* **288**, 2554–2560.
- Kris-Etherton PM, Yu-Poth S, Sabaté J, Ratcliffe HE, Zhao G & Etherton TD (1999) Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. *Am J Clin Nutr* **70**, 504S–511S.
- Kris-Etherton PM, Zhao G, Binkoski AE, Coval SM & Etherton TD (2001) The effects of nuts on coronary heart disease risk. *Nutr Rev* **59**, 103–111.
- Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y & Bostick RM (1996) Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med* **334**, 1156–1162.
- Lavedrine F, Zmirou D, Ravel A, Balducci F & Alary J (1999) Blood cholesterol and walnut consumption: a cross-sectional survey in France. *Prev Med* **28**, 333–339.
- Mann JI, Appleby PN, Key TJ & Thorogood M (1997) Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart* **78**, 450–455.
- Ros E, Nunez I, Perez-Heras A, Serra M, Gilbert R, Casals E & Deulofeu R (2004) A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. *Circulation* **109**, 1609–1614.
- Sabaté J (1999) Nut consumption, vegetarian diets, ischemic heart disease risk, and all-cause mortality: evidence from epidemiologic studies. *Am J Clin Nutr* **70**, 500S–503S.
- Sabaté J & Fraser GE (1994) Nuts: a new protective food against coronary heart disease. *Curr Opin Lipidol* **5**, 11–16.
- Sabaté J, Haddad E, Tanzman JS, Jambazian P & Rajaram S (2003) Serum lipid response to the graduated enrichment of a Step I diet with almonds: a randomized feeding trial. *Am J Clin Nutr* **77**, 1379–1384.
- Sabaté J, Radak T & Brown J (2001) The role of nuts in cardiovascular disease prevention. In *Handbook of Nutraceuticals and Functional Foods*, pp. 486–491 [R Wildman, editor]. Boca Raton: CRC Press.
- The Steering Committee of the Physicians' Health Research Group (1988) Findings from the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* **318**, 262–264.
- World Cancer Research Fund/American Institute for Cancer Research (1997) *Food, nutrition and the prevention of cancer: a global perspective*. Washington, DC: World Cancer Research Fund/American Institute for Cancer Research.