Vitamin E and heart disease: a case study[1,2]

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ABSTRACT The role of nutritional epidemiology studies in the development of nutritional recommendations has been controversial, in part because individual studies supporting either side of a given issue can often be identified. Several sets of criteria for inference of a causal relation between a dietary factor and a disease from epidemiologic studies have been suggested. One such set is that of Sir Austin Bradford Hill, which includes criteria such as strength of association, dose-response relation, consistency of association, temporally correct association, specificity of association, and biological plausibility. Another set of criteria, used by the US Preventive Services Task Force, ranks evidence according to study design, designating evidence from randomized controlled trials as superior to evidence from cohort or case-control studies, which are in turn superior to evidence from ecologic studies or opinions of respected authorities. The application of these criteria to the question of whether vitamin E intake is associated with coronary heart disease is examined here. It is suggested that the epidemiologic evidence from prospective cohort studies generally supports an inverse association of vitamin E intake and risk of coronary heart disease. The information available from randomized trials is limited but suggestive of an inverse association with nonfatal, but not with fatal, coronary events. It is suggested that the application of criteria for causal inference to specific questions in nutritional epidemiology may provide clarity to seemingly contradictory information. *Am J Clin Nutr* 1999;69(suppl):1322S–9S.

KEY WORDS α-Tocopherol, vitamin E, coronary heart disease, epidemiologic studies, prospective studies, causal inference

INTRODUCTION

The role of epidemiologic studies in developing and supporting nutritional recommendations is controversial, as the recent history of the formulation of the recommended dietary allowances (RDAs) by the National Research Council, who delayed the publication of the 10th revision of the RDAs for several years, illustrates. The delay was due in large part to an increase in epidemiologic literature in the 1980s that suggested that nutrients such as vitamins A and C may play important roles in preventing cancer and heart disease (1). When it was revealed that the Food and Nutrition Board was proposing to decrease the RDAs for these vitamins, concern was expressed that this might result in an increase in cancer rates several years or decades hence. Ultimately, there was little change in the RDAs for vitamins A and C. Ironically, the RDAs for folic acid were reduced by 50%, from 400 to 200 μg, between the 9th (2) and 10th (3) revision of the RDAs. In subsequent years it became widely accepted that inadequate folic acid intake is a major risk factor for neural tube defects at birth (4). Thus, the US Food and Drug Administration instituted a requirement that grain products be fortified with folic acid (5), and it is likely that in the next revision of the RDAs the recommended amounts of folic acid will be increased.

One set of criteria by which epidemiologic studies can be evaluated to determine whether there is sufficient evidence to infer a causal relation between dietary factors and risk of chronic diseases was outlined in the National Research Council's report *Diet and Health: Implications for Reducing Chronic Disease Risk* (1). In this report, the Committee on Diet and Health presented 6 of the criteria suggested by Hill (6) as a principal basis for evaluating the evidence. These are familiar to most students of epidemiology and are listed in **Table 1**. If causality can be inferred, then there is a basis for developing public health recommendations.

Another set of complementary criteria for determining whether evidence is sufficient to develop recommendations for disease prevention are those established by the US Preventive Services Task Force (7). These criteria focus on the design and quality of studies (Table 1). For example, if an association is established between a dietary exposure and disease outcome in a randomized, controlled trial, that is taken as the best evidence of causality to support development of recommendations. In the absence of randomized trials, evidence from analytic epidemiologic studies (ie, cohort or case-control studies) is considered to be the best source of information. In studies of dietary exposures, cohort studies—in which food intake is measured before onset of disease—are considered superior to case-control studies, because the latter may have biased conclusions because of differential recall of past dietary habits (8), although whether this occurs and has practical implications is controversial (9). The least impressive evidence to support recommendations would be opinions of experts or expert committees in the absence of adequate human studies.

In recent years there has been considerable interest in the possible role of dietary antioxidants in the etiology and prevention

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TABLE 1
Criteria for causal inference from epidemiologic studies

Hill criteria used by the Committee on Diet and Health[1]
1) Strength of association
2) Dose-response relation
3) Consistency of association
4) Temporally correct association
5) Specificity of association
6) Biological plausibility
Criteria used by the US Preventive Services Task Force[2]
I) Evidence obtained from at least one properly designed randomized controlled trial
II–1) Evidence obtained from well-designed controlled trials without randomization
II–2) Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
II–3) Evidence obtained from multiple time series with or without the intervention [dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence]
III) Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

[1] From reference 1 as adapted from Hill (6).
[2] From reference 7.

of coronary heart disease. Although many antioxidant compounds are found in the diet, vitamin E has been the focus of much of this research. This article is focused on the application of the Hill and US Preventive Services Task Force criteria to the association of dietary vitamin E (whether from food or supplements) and coronary heart disease. Note that this article is not meant to be a comprehensive review of this literature; for example, no studies related to plasma or tissue amounts of vitamin E and risk of coronary disease are included. Rather, it is intended as an illustration of how these criteria may be applied to determine causality while also showing the nature of the evidence related to a recommendation to consume vitamin E to prevent coronary heart disease.

HILL CRITERIA

Strength of association

The supposition behind this criterion is that the stronger the association—ie, the larger the size of the relative risk or odds ratio—the more likely the association is to be causal. Generally, the stronger an association is, the less likely it is to be explained by other confounding variables. Among the 6 prospective studies of vitamin E and coronary disease, 4 addressed the possible effect of vitamin E from foods (10–13) and 5 examined the effect of vitamin E from supplements (10, 11, 13–15). The relative risks for comparisons of the highest intake category from foods, supplements, or a combination of both with the lowest intake category in these 6 studies are presented in **Table 2**. Other characteristics of these 6 studies are also shown in this table.

The relative risk estimate for high vitamin E intake from foods in the 4 studies that addressed this association ranged from 0.95 to 0.35. The first of these relative risk estimates would be considered under any criteria to be an extremely weak association, whereas the latter is reasonably strong and, in the context of diet studies, quite striking. Expressed slightly differently, it is consistent with a 3-fold excess risk of coronary mortality in women who consumed low amounts of dietary vitamin E compared with women who consumed high amounts. This can be compared with a ≥10-fold relative risk of lung cancer mortality in those who smoke ≥1 pack cigarettes/d compared with nonsmokers in most prospective studies that reported on this association (16).

For vitamin E intake from supplements, the relative risk for those who had the highest reported dose of daily supplement intake compared with those who did not take vitamin E supplements ranged from 1.09 to 0.53. Another study reported a relative risk of 0.21 for supplement users compared with nonusers, but this estimate was not adjusted for potentially confounding variables (15). Thus, the strongest reported association corresponded to an approximate halving of the risk of coronary disease in those who took vitamin E supplements compared with those who did not.

Dose-response relation

Relative risk estimates of coronary heart disease with increasing intake of vitamin E, again from foods, supplements, or both combined are shown in **Table 3**. Four prospective studies presented data on foods that allowed investigation of the effect of dosage of vitamin E intake from foods, 3 presented information regarding dosage of supplemental vitamin E intake, and 2 compared those who took supplements with those who did not and presented no information on dosage.

Two of the studies provide results consistent with a dose-response relation (12, 13), with significant *P* values for the test for trend. For example, in a study conducted in Finland, there was a decreasing risk of coronary mortality in women with increasing vitamin E intake, with relative risks from lowest to highest thirds of vitamin E intake of 1.0, 0.73, and 0.35, respectively (12). In another study of postmenopausal women in Iowa, relative risks of coronary heart disease mortality from the lowest to highest fifths of vitamin E intake were 1.0, 0.70, 0.76, 0.32, and 0.38, respectively (13).

Of the other 2 studies, one somewhat supported an inverse association of dietary vitamin E and risk of coronary disease, with the relative risk of 0.79 for a comparison of the highest fifth of intake with the lowest; however, there was no clear dose-response relation, and relative risks from lowest to highest fifths were 1.0, 1.10, 1.17, 0.97, and 0.79 (11). The other study did not support an association of dietary vitamin E intake with coronary disease (10). However, this latter study was based on a food-frequency questionnaire that listed about half as many food items as did the questionnaires in the other 3 studies, and it may not have accurately assessed individual vitamin E intake from foods.

None of the studies strongly supported a dose-response relation for supplemental intake with coronary disease. In 2 of the studies it appeared that although intake of any supplements (except for low doses) was inversely associated with risk of coronary disease, there was little evidence of a dose response (10, 11). For example, in a study of female nurses, relative risks of coronary disease were 0.56, 0.56, and 0.58 in those taking daily doses of 100–250, 300–500, and ≥600 IU (1 IU = 1 mg α-TE), respectively, compared with those who did not take supplements (10). In the other study, the relative risks of coronary disease in male health professionals in the highest 3 categories of supplemental intake compared with those who took no supplements were 0.78, 0.54, and 0.70 (11). The third study with dose information did not observe an association of vita-

TABLE 2
Association of vitamin E intake and relative risk (RR) of coronary heart disease in prospective epidemiologic studies

Vitamin E source and study	Cohort	Age range at baseline	Study period	CHD Events	RR (95% CI)[1]	*P* for trend
		y		*n*		
Intake from foods						
Stampfer et al (10)	87 245 Female nurses	34–59	1980–1988	552 Events	0.95 (0.72, 1.23)[2]	0.99
Rimm et al (11)	17 916 Male health professionals	40–75	1986–1990	393 Events	0.79 (0.54, 1.15)	0.11
Knekt et al (12)	2748 Finnish men	30–69	1966–1984	186 Deaths	0.68 (0.42, 1.11)	0.01
	2385 Finnish women			58 Deaths	0.35 (0.14, 0.8)	<0.01
Kushi et al (13)	19 687 Iowa women	55–69	1986–1992	138 Deaths	0.38 (0.18, 0.80)	0.004
Intake from supplements						
Stampfer et al (10)	87 245 Female nurses	34–59	1980–1988	552 Events	0.63 (0.45, 0.88)[2]	—
				440 Events[3]	0.54 (0.36, 0.82)[2]	—
Rimm et al (11)	39 910 Male health professionals	40–75	1986–1990	667 Events	0.70 (0.55, 0.89)[4]	0.22
Kushi et al (13)	34 486 Iowa women	55–69	1986–1992	242 Deaths	1.09 (0.67, 1.77)[4]	0.39
Losonczy et al (14)	11 178 US residents of four areas	67–105	1984–1993	1101 Deaths	0.53 (0.34, 0.84)	—
Meyer et al (15)	2000 Quebec City men	<50–>60	1985–1991	100 Events	0.21[5]	—
Intake from foods and supplements combined						
Stampfer et al (10)	87 245 Female nurses	34–59	1980–1988	552 Events	0.66 (0.50, 0.87)[2]	<0.001
Rimm et al (11)	39 910 Male health professionals	40–75	1986–1990	667 Events	0.60 (0.49, 0.83)	0.01
Kushi et al (13)	34 486 Iowa women	55–69	1986–1992	242 Deaths	0.96 (0.62, 1.51)	0.27

[1] Adjusted for multiple coronary heart disease risk factors unless otherwise noted.
[2] Adjusted for age and smoking.
[3] After excluding events in the first 2 y of follow-up.
[4] Comparison of subjects in the highest intake category (≥250 IU/d) with those not taking supplements.
[5] Crude RR ($P < 0.05$).

min E supplement intake with mortality from coronary heart disease (13).

Temporally correct association

The studies presented in Tables 2 and 3 are all prospective cohort studies; participants with coronary disease at baseline were excluded from follow-up. Thus, in each of these studies, dietary habits were assessed before the occurrence of disease or death, and the results of these studies are directly relevant to the question of whether vitamin E intake influences the risk of subsequent coronary heart disease. As noted below, results from these studies are consistent with the theory that vitamin E intake from foods and supplements is associated with decreased risk of coronary heart disease.

Not all studies of diet and coronary disease satisfy this criterion, however. One example is the Scottish Heart Health Study, a cross-sectional survey of diet and coronary disease in 10 359 men and women (17). In this study, dietary habits were assessed in participants by using a 50-item food-frequency questionnaire. Participants were classified as having diagnosed coronary heart disease if they reported that they had medically diagnosed angina or myocardial infarction. They were classified as having undiagnosed coronary heart disease if they answered appropriately on the angina questionnaire of Rose et al (18) or if they had abnormal electrocardiograph results. All remaining participants were classified as control subjects. Dietary habits, including vitamin E intake, were then compared among the 3 groups.

The investigators in this study recognized that study participants with diagnosed coronary heart disease had probably modified their diets as a result of their diagnosis; however, they suggested that comparisons between the undiagnosed coronary disease group and the control subjects may reflect etiologically meaningful differences (17). For vitamin E intake, for example, the odds ratio for diagnosed coronary heart disease increased significantly with increasing vitamin E intake, whereas the odds ratio for undiagnosed coronary heart disease decreased modestly with increasing vitamin E intake (17). However, participants, including those with undiagnosed coronary heart disease, may have altered their diets as a result of their symptoms, and thus this study is inadequate for providing support for causality.

Consistency of association

Generally, the more studies that observe a similar relation between an exposure and disease, preferably in different study populations and perhaps with different study designs, the more likely it is that the association is causal. The information in Tables 2 and 3 can be examined to determine whether there is consistency of the association of vitamin E with coronary heart disease among the prospective cohort studies that have examined this relation. Among the 4 studies and 5 cohorts to report associations of vitamin E intake from foods and coronary heart disease, only one, the Nurses' Health Study (10), did not suggest an inverse association of vitamin E intake with coronary heart disease incidence (Table 2). Among the studies reporting on the association of supplemental vitamin E intake, only one, the Iowa Women's Health Study (13), did not suggest an inverse association of supplemental vitamin E with coronary disease. In the Nurses' Health Study, vitamin E from foods was not inversely associated with coronary disease, but supplemental vitamin E was; conversely, in the Iowa study, vitamin E from foods but not supplements was inversely associated with coronary heart disease. Thus, overall, among the 6

TABLE 3
Relative risk (RR) of coronary heart disease across increasing categories of vitamin E intake in prospective cohort studies by source

Vitamin E source and study	Category of intake					*P* for trend
	1 (Lowest)	2	3	4	5 (Highest)	
Intake from foods						
Stampfer et al (10)						
Intake (IU/d)[1]	0.3–3.1	3.2–3.9	4.0–4.8	4.9–6.2	6.3–100	
RR (95% CI)	1.0	1.04 (0.80, 1.35)	0.87 (0.66, 1.14)	1.14 (0.89, 1.47)	0.95 (0.72, 1.23)	0.99
Rimm et al (11)						
Intake (IU/d)	1.6–6.9	7.0–8.1	8.2–9.3	9.4–11.0	≥11.1	
RR (95% CI)	1.0	1.10 (0.80, 1.51)	1.17 (0.84, 1.62)	0.97 (0.69, 1.37)	0.79 (0.54, 1.15)	0.11
Knekt et al (12)						
Intake (IU/d)	≤6.8	6.9–8.9	>8.9	—	—	
RR (95% CI): men	1.0	0.97 (0.67, 1.40)	0.68 (0.42, 1.11)	—	—	0.01
RR (95% CI): women	1.0	0.73 (0.38, 1.39)	0.35 (0.14, 0.88)	—	—	<0.01
Kushi et al (13)						
Intake (IU/d)	≤4.9	4.9–6.2	6.3–7.6	7.6–9.6	≥9.6	
RR (95% CI)	1.0	0.70 (0.41–1.18)	0.76 (0.44, 1.29)	0.32 (0.17, 0.63)	0.38 (0.18, 0.80)	0.004
Intake from supplements						
Stampfer et al (10)						
Intake (IU/d)	None	<100	100–250	300–500	≥600	
RR (95% CI)	1.0	0.93 (0.23, 3.75)	0.56 (0.21, 1.51)	0.56 (0.33, 0.96)	0.58 (0.24, 1.42)	NS
Rimm et al (11)						
Intake (IU/d)	None	<25	25–99	100–249	≥250	
RR (95% CI)	1.0	0.85 (0.69, 1.05)	0.78 (0.59, 1.08)	0.54 (0.33, 0.88)	0.70 (0.55, 0.89)	0.22
Kushi et al (13)						
Intake (IU/d)	None	≤25	26–100	101–250	>250	
RR (95% CI)	1.0	0.83 (0.54, 1.28)	0.95 (0.56, 1.59)	1.25 (0.58, 2.68)	1.09 (0.67, 1.77)	0.39
Intake from foods and supplements combined						
Stampfer et al (10)						
Intake (IU/d)	1.2–3.5	3.6–4.9	5.0–8.0	8.1–21.5	21.6–1000	
RR (95% CI)	1.0	1.00 (0.78, 1.28)	1.15 (0.90, 1.48)	0.74 (0.57, 0.98)	0.66 (0.50, 0.87)	<0.001
Rimm et al (11)						
Intake (IU/d)[1]	6.4	8.5	11.2	25.2	419	
RR (95% CI)	1.0	0.89 (0.69, 1.05)	0.81 (0.59, 1.08)	0.71 (0.33, 0.88)	0.60 (0.55, 0.89)	0.01
Kushi et al (13)						
Intake (IU/d)	≤5.7	5.7–7.8	7.8–12.2	12.2–35.6	≥35.6	
RR (95% CI)	1.0	1.05 (0.69, 1.69)	0.52 (0.31, 0.87)	0.68 (0.41, 1.10)	0.96 (0.62, 1.51)	0.27

[1] 1 IU = 1α-TE.
[2] Median intake in category.

prospective studies to examine the association of vitamin E intake with coronary disease, all reported some evidence of an inverse association of some measure of vitamin E intake with risk of coronary disease.

Specificity of association

In all but one of the studies listed in Table 2, the reported associations of vitamin E with coronary heart disease were adjusted for several other coronary heart disease risk factors. Thus, the association was generally independent of other known and measured risk factors for coronary heart disease. However, in only 2 of the studies was information available on blood cholesterol concentrations, a known risk factor for coronary heart disease (12, 15); in one of these, only crude associations of vitamin E intake with coronary mortality were presented (15).

Coronary heart disease is recognized as a multifactorial disease entity. Among dietary factors, dietary cholesterol (10, 19, 20), various fatty acids (21, 22), and dietary fiber (20, 23, 24) have been recognized as factors that influence the risk of coronary heart disease. Similarly, vitamin E and possibly other vitamins and minerals may influence the risk of coronary heart disease. Vitamin E may also influence the risk of other diseases, including cancer (25).

In studies of dietary factors and chronic diseases such as coronary heart disease, the criterion of specificity of association is rarely met. A specific factor such as inadequate vitamin E intake is not the only cause of the disease, and coronary heart disease is not necessarily the only consequence of low vitamin E intakes. However, this also holds for well-established risk factors for coronary heart disease, such as cigarette smoking. Heart disease risk may still be elevated for other reasons in nonsmokers, and cigarette smoking is recognized as a cause of several other illnesses. Thus, in the context of chronic diseases with multifactorial etiologies, failure to meet the Hill criterion of specificity of association does not necessarily mitigate inference that an association is causal.

For dietary variables, the ability to ascribe specificity of an association to a given dietary factor is complicated by the multicollinearity inherent in dietary exposures. Specifically, nutrients and other dietary factors are usually consumed as foods rather than as discrete items. For example, foods that are high in vitamin E also tend to be high in polyunsaturated fatty acids.

Thus, associations that are observed for vitamin E may be results of other dietary factors. Although this multicollinearity is avoided to a large extent in studies of supplements, confounding by other factors that may by correlated with supplement-taking behavior may remain.

Biological plausibility

It is increasingly being recognized that oxidized LDL has greatly enhanced ability to infiltrate the subendothelial layer of arteries and that this oxidative modification also enhances the uptake of LDL by macrophages, thereby creating foam cells (26). Factors that may prevent the oxidative modification of LDL may therefore inhibit the development of foam cells, fatty streaks, atherosclerosis, and coronary heart disease. Vitamin E is a potent lipid-soluble antioxidant that is carried in lipoproteins; this provides a plausible biological mechanism by which increased vitamin E intake may decrease risk of coronary heart disease. High levels of vitamin E intakes may result in high concentrations of vitamin E in lipoprotein particles, thereby inhibiting oxidative modification of these lipoproteins.

Although there are plausible biological mechanisms by which vitamin E may decrease risk of coronary heart disease, it should be stressed that recognition of biological mechanisms does not adequately determine that a causal association exists. The β-carotene drama provides a cautionary tale in this regard. There were biologically plausible mechanisms for a protective effect of β-carotene on carcinogenesis related to its antioxidant capabilities and its role as a precursor of vitamin A (25). There was also supporting epidemiologic evidence from case-control studies of vegetable and fruit intake showing that high β-carotene intake was associated with decreased risk of lung cancer (27) and from nested case-control studies comparing blood concentrations of β-carotene in people who subsequently developed lung cancer with those in the same cohort who did not (28). However, in 2 of 3 large, randomized trials of β-carotene supplementation and lung cancer risk, subjects randomly assigned to receive β-carotene supplementation had a higher rate of lung cancer than did control subjects (29, 30). In the other study, there was no significant difference in lung cancer rates between treatment groups (31). This suggests that evidence from studies of different design, not just case-control or prospective studies, may be required to establish causality.

US PREVENTIVE SERVICES TASK FORCE CRITERIA

In its criteria, the US Preventive Services Task Force explicitly recognizes different study designs as a basis for determining the quality of evidence for inferring causality. Whereas the previous discussion focused almost exclusively on prospective cohort studies, other studies using other designs have examined the association of vitamin E intake and coronary heart disease risk.

Criterion I: evidence obtained from at least one properly designed randomized controlled trial

Only 1 randomized, controlled trial of vitamin E intake and primary prevention of coronary heart disease has been published. This study is the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a randomized, placebo-controlled trial of α-tocopherol and β-carotene in 29 133 male cigarette smokers in Finland (29). Approximately equal numbers of participants were randomly assigned to one of 4 groups: those who received vitamin E supplements (50 mg/d) alone, those who received β-carotene supplements (20 mg/d) alone, those who received vitamin E and β-carotene, and those who received placebo. Of relevance to the vitamin E–related analyses, 14 564 men received vitamin E supplements and 14 569 did not. Results for different endpoints in the ATBC Study and from a secondary prevention trial (32) are shown in **Table 4**.

Participants in the ATBC Study were enrolled from 1985 to 1988 and were followed for 5–8 y. Although the endpoint that garnered the most attention in this study was the increased rate of lung cancer in those receiving β-carotene supplements, the investigators also examined the effect of the intervention agents on other endpoints, including coronary heart disease mortality and other cardiovascular mortality endpoints (29). Of the men who received vitamin E supplements, 602 died of coronary heart disease (mortality rate of 71/10 000 person-years of follow-up). Among those who did not receive vitamin E supplements, there were 637 coronary heart disease deaths (mortality rate of 75/10 000 person-years). Although the vitamin E group experienced a slightly lower death rate from coronary heart disease, this was modest and was offset by somewhat higher mortality rates from cancer and hemorrhagic stroke.

In addition to effects on mortality, the effects of vitamin E and β-carotene supplements on occurrence of angina pectoris were also examined in the ATBC Study (33). In these analyses, 6864 men with evidence of coronary heart disease at baseline who were excluded from analysis were evenly distributed among the study's 4 treatment groups. As with coronary mortality, men who received vitamin E supplements were at slightly reduced risk of angina compared with those who did not, with a relative risk of 0.91. This relative risk was attenuated to 0.97 when differences in rates of angina were compared between those who received only vitamin E and those who received placebo because men who received β-carotene supplementation experienced a slightly higher rate of angina pectoris than those who did not receive β-carotene. Overall, this study provides only modest evidence in support of a protective effect of vitamin E supplements against coronary heart disease.

There have been at least 2 secondary prevention trials of vitamin E supplementation and coronary heart disease. One of these was an analysis in the ATBC Study of the men with baseline evidence of myocardial infarction; 1862 such men were randomly assigned in roughly equivalent numbers to the 4 study treatments (34). Overall, the men who received only vitamin E supplements experienced a significantly reduced rate of recurrence of myocardial infarction compared with those who received placebo alone, with a relative risk of 0.62. However, this was offset by a nonsignificant increase in fatal coronary heart disease (relative risk: 1.33), which resulted in a modest, nonsignificant decrease in total coronary events in the vitamin E–supplemented group (relative risk: 0.90). Men who received either β-carotene alone or a combination of vitamin E and β-carotene had nonsignificantly increased risks of total coronary events compared with those who received placebo.

The other secondary prevention trial was the Cambridge Heart Antioxidant Study (CHAOS), a randomized, double-blind, placebo-controlled study of 2002 patients with angiographically proven coronary atherosclerosis (32). In this study, 1035 patents were randomly assigned to receive intervention of either 800 or 400 IU vitamin E/d; results were apparently similar for these 2 doses. As in the ATBC Study, those who received vitamin E experienced a significantly reduced risk of developing nonfatal myocardial infarction compared with those who

TABLE 4
Randomized trials of vitamin E supplementation and coronary heart disease[1]

Study, dose, and randomization	Population	Age at baseline	Length of follow-up	Outcome measured	Events	RR[2] (95% CI)
		y	*y*		*n*	
Primary prevention trials						
ATBC Group (29)	29 133 Male smokers	50–69	5–8			
50 mg (*n* = 14 564)				CHD death	602	—
Control (*n* = 14 569)				CHD death	637	
Rapola et al (33)	22 269 Male smokers free of CHD	50–69	4–7			
50 mg (*n* = 11 118)				Angina pectoris	948	0.91 (0.83, 0.99)
Control (*n* = 11 151)				Angina pectoris	1035	
50 mg (*n* = 5570)				Angina pectoris	476	0.97 (0.85, 1.10)
Placebo (*n* = 5602)				Angina pectoris	487	
Secondary prevention trials						
Stephens et al (32)	2002 Patients with known coronary atherosclerosis	61.8[3]	0–2.7			
400 or 800 IU (*n* = 1035)				Major CVD	41	0.53 (0.34, 0.83)
Placebo (*n* = 967)				Major CVD	64	
400 or 800 IU (*n* = 1035)				Nonfatal MI	14	0.23 (0.11, 0.47)
Placebo (*n* = 967)				Nonfatal MI	41	
400 or 800 IU (*n* = 1035)				CVD death	27	1.18 (0.62, 2.27)
Placebo (*n* = 967)				CVD death	23	
Rapola et al (34)	1862 Male smokers with previous MI	50–69	5–8			
50 mg (*n* = 963)				Major CHD	217	0.97 (0.80, 1.19)
Control (*n* = 899)				Major CHD	207	
50 mg (*n* = 963)				Nonfatal MI	96	0.89 (0.67, 1.20)
Control (*n* = 899)				Nonfatal MI	94	
50 mg (*n* = 963)				CHD death	121	1.05 (0.80, 1.37)
Control (*n* = 899)				CHD death	113	
Rapola et al (34)	904 male smokers with previous MI	50–69	5–8			
50 mg (*n* = 466)				Major CHD	94	0.90 (0.67, 1.22)
Placebo (*n* = 438)				Major CHD	94	
50 mg (*n* = 466)				Nonfatal MI	40	0.62 (0.41, 0.96)
Placebo (*n* = 438)				Nonfatal MI	55	
50 mg (*n* = 466)				CHD death	54	1.33 (0.86, 2.05)
Placebo (*n* = 438)				CHD death	39	
50 mg (*n* = 466)				All MI	64	0.81 (0.56, 1.17)
Placebo (*n* = 438)				All MI	66	
50 mg (*n* = 466)				Fatal MI	24	1.83 (0.85, 3.95)
Placebo (*n* = 438)				Fatal MI	11	

[1] ATBC Group, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group; RR, relative risk; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.
[2] Relative risk (and 95% CI) comparing vitamin E–supplemented group with control or placebo group.
[3] $\bar{x}$.

received placebo (relative risk: 0.23), whereas the risk of fatal myocardial infarction and total cardiovascular deaths (relative risk: 1.18) was elevated in this group. Overall, the vitamin E–supplemented group had a reduced risk of cardiovascular deaths or nonfatal myocardial infarction of 0.53 ($P < 0.005$).

The general impression from these randomized trials is that there may be some influence of vitamin E supplementation on reducing risk of coronary events, particularly nonfatal events, but that the evidence is modest. The strongest evidence comes from CHAOS, but in this study of secondary prevention there

was an elevated risk of fatal endpoints (32). Although this increased coronary mortality rate may have been due to chance, the fact that the ATBC Study also reported an elevated risk of coronary mortality with vitamin E supplementation suggests caution in dismissing this finding. In the only primary prevention study to date, vitamin E supplements appear to have had only a modest effect on decreasing occurrence of either angina or fatal coronary heart disease (29). Other studies of vitamin E supplementation and coronary heart disease are currently underway (35), but none are aimed at increasing vitamin E intake from foods. The Women's Health Initiative, perhaps the only major ongoing dietary intervention trial that has the ability to examine the primary prevention of coronary heart disease, has as its dietary intervention focus a low-fat diet (36). Because the richest dietary sources of vitamin E are oil-rich foods from vegetable sources, the intervention group in this trial may inadvertently be consuming lower amounts of vitamin E than the comparison group if the dietary intervention focuses on reduction of all fats in the diet without attention to the type or source of fat. In any case, the trial is not designed to examine the effect of alterations in vitamin E intake on risk of coronary heart disease.

Criterion II

Evidence obtained from well-designed controlled trials without randomization.

No controlled trials without randomization regarding the association of vitamin E and coronary heart disease have been published.

Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Several prospective cohort studies have published results directly pertaining to the question of whether vitamin E intake, from foods or supplements, is associated with risk of coronary heart disease. As shown in Table 2, most of the studies noted an inverse association. Although 2 of the 6 studies were from the same research group (10, 11) and a third (13) used a dietary assessment instrument similar to that used in the former 2, other studies have been conducted in other populations. The largest studies were the 3 that assessed dietary and supplemental vitamin E intake using similar food-frequency questionnaires (10, 11, 13).

Case-control studies of diet and disease may be influenced by differential measurement error (8) and therefore are generally considered to be a weaker basis on which to make causal inferences regarding dietary factors. Few such studies of diet and heart disease have been conducted.

Evidence obtained from multiple time series with or without the intervention.

At least one international correlation study examined the association of food disappearance data from the Food and Agricultural Organization with premature mortality from coronary heart disease (37). This study included 24 developed countries, 19 of which were European. Of the various commodities and nutrients examined, vitamin E showed among the strongest inverse associations, with a correlation of −0.8. Within each country, changes in vitamin E availability and changes in coronary heart disease mortality from 1970 to 1987 supported an inverse association between these 2 variables.

There has also been at least one ecologic study of the association of plasma vitamin E concentrations and mortality from coronary heart disease in several European populations that are participants in the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO/MONICA) Study (38). In this study, populations with the highest mortality rates from coronary heart disease had the lowest plasma concentrations of vitamin E, which supports an inverse association of vitamin E with coronary mortality.

Criterion III: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

No expert committee has as yet pronounced definitively that vitamin E is inversely associated with coronary heart disease and that increased vitamin E intake or ingestion of vitamin E supplements is a recommended course of action for the prevention of coronary heart disease. However, listed in the American Heart Association's top 10 heart and stroke research advances for 1996 is "Vitamin E may prevent heart disease" (American Heart Association Office of Communications, December 18, 1996). Studies that were specifically mentioned in this designation were the secondary prevention trial CHAOS (32) and the Iowa Women's Health Study (13), one of the prospective cohort studies.

SUMMARY

There is a growing body of epidemiologic literature on the relation between vitamin E intake and coronary heart disease. Several prospective cohort studies have been published on this topic, and they generally support an inverse association of vitamin E intake and coronary heart disease morbidity or mortality. Although evidence for a dose-response relation is somewhat lacking, the consistency of findings across the cohort studies increases the confidence that this association may be causal.

To date, only 2 randomized trials, both using vitamin E supplements, have addressed the question of whether vitamin E intake may be related to coronary heart disease (29, 32). One of these, the ATBC Study, a primary prevention trial in male smokers, provided little evidence that vitamin E intake may decrease the incidence of angina pectoris or mortality rates from coronary heart disease (29, 33). The other trial, a secondary prevention trial, provided evidence that vitamin E supplements may decrease risk of recurrence of nonfatal myocardial infarction, but not fatal cardiovascular events (32). In a follow-up of subjects with definite myocardial infarction at entry into the ATBC Study, similar findings were also observed (34). Overall, these studies, although perhaps broadly consistent with an inverse association of vitamin E intake with coronary disease, are neither definitive nor convincing in this matter.

The use of the Hill criteria to examine whether there is evidence of a causal relation between vitamin E and coronary heart disease shows that there is some consistency among the results of the prospective cohort studies, with all of them suggesting that vitamin E intake from foods or from supplements is inversely associated with risk of coronary disease. However, the evidence for a dose-response relation is less consistent among the studies, whereas the strength of association is modest although relatively strong for associations of dietary factors with chronic disease endpoints. Plausible biological mechanisms related to prevention of oxidative modification of LDL are based on numerous labora-

tory studies examining the role of vitamin E and other antioxidants in atherogenesis.

Following the US Preventive Services Task Force criteria, there is little evidence from randomized trials that vitamin E supplementation may reduce risk of coronary heart disease, although it may play a role in prevention of nonfatal myocardial infarction in those with coronary heart disease. Evidence from prospective cohort studies is reasonably strong and consistent, and the one ecologic study to examine associations of food availability and coronary heart disease rates is consistent with an inverse association of vitamin E and coronary heart disease. Few case-control studies and no pronouncements from expert committees exist on this topic. Overall, the evidence can be deemed to support an inverse association of vitamin E intake and coronary heart disease. Whether there is sufficient evidence on which to base public health nutrition recommendations is a matter of debate.

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