

A Systematic Review of the Evidence Supporting a Causal Link Between Dietary Factors and Coronary Heart Disease

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Background: Although a wealth of literature links dietary factors and coronary heart disease (CHD), the strength of the evidence supporting valid associations has not been evaluated systematically in a single investigation.

Methods: We conducted a systematic search of MEDLINE for prospective cohort studies or randomized trials investigating dietary exposures in relation to CHD. We used the Bradford Hill guidelines to derive a causation score based on 4 criteria (strength, consistency, temporality, and coherence) for each dietary exposure in cohort studies and examined for consistency with the findings of randomized trials.

Results: Strong evidence supports valid associations (4 criteria satisfied) of protective factors, including intake of vegetables, nuts, and "Mediterranean" and high-quality dietary patterns with CHD, and associations of harmful factors, including intake of *trans*-fatty acids and foods with a high glycemic index or load. Among studies of higher methodologic

quality, there was also strong evidence for monounsaturated fatty acids and "prudent" and "western" dietary patterns. Moderate evidence (3 criteria) of associations exists for intake of fish, marine ω -3 fatty acids, folate, whole grains, dietary vitamins E and C, beta carotene, alcohol, fruit, and fiber. Insufficient evidence (≤ 2 criteria) of association is present for intake of supplementary vitamin E and ascorbic acid (vitamin C); saturated and polyunsaturated fatty acids; total fat; α -linolenic acid; meat; eggs; and milk. Among the dietary exposures with strong evidence of causation from cohort studies, only a Mediterranean dietary pattern is related to CHD in randomized trials.

Conclusions: The evidence supports a valid association of a limited number of dietary factors and dietary patterns with CHD. Future evaluation of dietary patterns, including their nutrient and food components, in cohort studies and randomized trials is recommended.

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THE RELATIONSHIP BETWEEN dietary factors and coronary heart disease (CHD) has been a major focus of health research for almost half a century. The pioneering work of Keys and Aravanis¹ stimulated many subsequent studies of diet and CHD, which have since evaluated the effects of numerous dietary nutrients, foods, and dietary patterns on CHD risk. More recently, prospective cohort studies and randomized controlled trials (RCTs) have examined these associations in large populations with long periods of follow-up. However, the results of cohort studies and RCTs can be discrepant (eg, for intake of vitamin E and beta carotene),²⁻¹³ and the results of some RCTs of dietary supplements paradoxically revealed adverse effects on CHD for certain nutrients that were previously shown to exert protective effects in cohort studies.^{2,4,7,8} This has generated confusion among health care professionals, policy makers, and the population at large who are interested in

this information to aid them in CHD prevention strategies.

In his classic study, Hill¹⁴ proposed a set of criteria (the Bradford Hill criteria) to evaluate systematically whether a causal link between an exposure of interest and a health outcome exists. These guidelines are used by epidemiologists to test causal hypotheses and have undergone little modification since their original publication.¹⁵ Before advocating that specific dietary factors be consumed in large or minimal amounts, it is necessary to base public health recommendations on the best available scientific evidence.¹⁶ To address this issue, we conducted a systematic review of the literature examining the association between nutrient intake, dietary components, and dietary patterns (hereafter referred to as dietary exposures) and CHD and its related clinical outcomes. Our specific objectives were (1) to systematically evaluate dietary exposures and CHD using the Bradford Hill criteria; (2) to determine which dietary exposures have been studied sufficiently in RCTs and found to support the findings of

prospective cohort studies; and (3) to identify the dietary exposures deemed to have insufficient evidence to be conclusive.

METHODS

SEARCH STRATEGY AND STUDY SELECTION

We searched the MEDLINE database for prospective cohort studies and RCTs from 1950 through June 2007. The bibliographies of retrieved articles were scanned for additional cohort studies and RCTs. Two of us (A.M. and L.D.) independently assessed study eligibility. Excluded studies and reasons for exclusion were listed, and disagreement was resolved by discussion and consensus. We included original English-language articles pertaining to the effect of diet on the following primary outcomes: coronary or ischemic heart disease and fatal or non-fatal myocardial infarction. These articles were also evaluated for the following secondary outcomes: angina pectoris, sudden death, cardiovascular disease, and total mortality. Relative risks (RRs) of outcomes are presented with their 95% confidence intervals (CIs) after adjusting for potential confounders. We only considered studies that followed up subjects for at least 1 year. Cohort studies had to include estimates of dietary intake using conventional dietary assessment tools (eg, food frequency questionnaires, food records, or 24-hour diet recall). Clinical trials had to be randomized and to compare dietary exposure with a control diet or a placebo. Crossover trials were excluded if plasma biomarkers or atherosclerotic indicators were not evaluated because coronary outcomes occurring after a crossover would be difficult to interpret.

DATA EXTRACTION

The following data were extracted from the selected studies: (1) study design (cohort study or RCT, ie, parallel or factorial); (2) country of origin; (3) number of participants; (4) characteristics of participants (ie, age and sex); (5) dietary assessment tool; (6) intake dosage; (7) length of follow-up; (8) description of the interventions (RCTs); and (9) cardiovascular disease outcomes.

For the prospective cohort studies, data were extracted on the estimates of the association between the dietary exposure and disease outcome. The cohort studies typically report estimated intake as quantiles (usually quartiles or quintiles). The higher intake level is compared with the lowest intake level and the

results are reported as odds ratios or RRs for each clinical outcome. The *P* values for trend, where available, were used to evaluate dose-response relationships. For RCTs, we compared the RRs of disease outcomes between the dietary intervention and control groups. The cohort studies and RCTs were stratified according to risk of bias (methodologic quality), as determined using the criteria in supplementary appendix 1 (this and the other appendices are available on request from the authors).^{17,18} The different dietary patterns evaluated in studies were noted. The "Mediterranean" dietary pattern emphasizes a higher intake of vegetables, legumes, fruits, nuts, whole grains, cheese or yogurt, fish, and monounsaturated relative to saturated fatty acids. The "prudent" dietary pattern is characterized by a high intake of vegetables, fruit, legumes, whole grains, and fish and other seafood. The "western" pattern is characterized by a high intake of processed meat, red meat, butter, high-fat dairy products, eggs, and refined grains.

APPLICATION OF BRADFORD HILL GUIDELINES

A modified algorithm of the Bradford Hill criteria was used to systematically evaluate the evidence of a causal relationship between each dietary exposure and CHD.¹⁴ As summarized in **Table 1**, the following 4 criteria were used in the review of cohort studies: strength, consistency, temporality, and coherence. A fifth criterion, biological gradient, was not included in the algorithm because dietary exposures may not exhibit dose-response relationships with CHD owing to possible threshold effects or "j-shaped" relationships (Table 1). Nevertheless, we explored evidence of this criterion separately.

The 4 Bradford Hill criteria were used to derive a causation score for each dietary exposure. The score was computed as the unweighted sum of the number of criteria that were met, for a possible range of 0 to 4. A score of 4 was considered strong evidence of a cause-and-effect relationship between the dietary exposure and disease. A score of 3 was deemed to indicate moderate evidence of causation. A score of 2 or less was considered a reflection of weak evidence of causation. As a final step, a sixth criterion, experiment, was used to examine whether the evidence from cohort studies was consistent with that from RCTs. Three criteria were omitted, including plausibility, specificity, and analogy because these factors were already satisfied by default (plausibility), considered non-specific to CHD (specificity), or deemed to be subjective (analogy) (Table 1).

STATISTICAL ANALYSES

We used commercially available statistical software (Comprehensive Meta Analysis software, version 2.2 [Biostat, Englewood, New Jersey] and SAS, version 9.1 [SAS Institute Inc, Cary, North Carolina]). Statistical heterogeneity across studies was assessed using the *Q* statistic,¹⁹ with significant heterogeneity for all of the dietary predictors except for beta carotene, eggs, monounsaturated fatty acids, *trans*-fatty acids, nuts, whole grains, and a "Mediterranean" dietary pattern. Summary estimates were calculated using a general variance-based method (random-effects model) with 95% CIs.¹⁹ Because the potential confounders considered in multivariate analyses vary across studies, we used the parameter estimates in the most complex model, which typically include demographic, lifestyle, and dietary factors. Stratified analyses were also conducted by methodologic quality, sex, type of dietary assessment tool (food frequency questionnaires vs food records and 24-hour recall), continental region (North America, Europe, and Asia), and type of prevention strategy (primary vs secondary) to assess the influence of these factors on the observed associations between diet and CHD.

INVESTIGATION OF HETEROGENEITY

The comparison of quantile extremes to compute RRs in cohort studies may add heterogeneity to summary RR estimates because the mean and median levels of intake in the quantile groups varied from study to study. To examine this, we created a scatterplot and linear regression for each dietary exposure, with the RR value for a given study on the *y*-axis and the difference in mean or median intake between quantile extremes on the *x*-axis. A slope of greater than or less than 0 would suggest that the differences in mean intake across studies influenced the summary RR value, whereas a slope of 0 would suggest that differences in mean intake across studies probably have a negligible effect on the summary estimates. As shown in supplementary appendix 2, no relationship was observed for ω -3 fatty acids (as well as other dietary exposures; data not shown), suggesting that different quantile values across studies likely cannot explain the variation in RR values. Finally, to assess whether the results might be explained by certain dietary factors being studied more frequently or the possible reporting of mostly positive results, we examined the relationship between the summary RR val-

Table 1. Bradford Hill Criteria for Assessing Causation in Cohort Studies and Definitions Used in This Review

Criterion (No.)	Bradford Hill Criteria (1965)	Definition in This Review
Included in causation score		
Strength (1)	Most important factor; RR needed to define a strong association likely depends on phenomena being studied	Strong association for each dietary exposure was defined as summary RR of ≤ 0.83 or ≥ 1.20 , statistically significant at $P < .05$, and in expected direction ^{a,b}
Consistency (2)	Finding of an association needs to be replicated in other studies	Consistency for each dietary exposure was defined as $\geq 67\%$ of associations ^c showing strong ^d or modest ^e effect on primary outcomes in expected direction for dietary exposure in question ^b
Temporality (3)	Refers to temporal relationship of association between exposure and disease outcome; to infer causality, exposure must precede outcome	Measurement design of each observational study was temporally correct because analyses were restricted to prospective cohort studies, which ensured absence of outcomes at start of follow-up ^f
Coherence (4)	Cause-and-effect relationship should not conflict with known information on natural history and biology of disease (eg, consistent with sex differences, secular trends, geographic findings, histopathologic/laboratory studies, animal models)	Evidence needs to support an association of dietary exposure with surrogate risk factors for atherosclerosis or MI, or subclinical markers of atherosclerosis, or significant summary RR showing an association with primary outcomes in expected direction
Evaluated separately from causation score		
Biological gradient (5)	When risk of disease increases (or decreases) incrementally as dose of exposure increases; provides strong evidence of causal relationship	Biological gradient of each dietary predictor was defined as $\geq 50\%$ of tests for trend ^c pertaining to primary outcomes being statistically significant in expected direction for exposure in question ^b
Examined if RCTs support evidence of causation		
Experiment (6)	Experimental evidence from laboratory studies or RCTs could potentially provide strongest support for causation	Experimental evidence of each dietary exposure was defined as $\geq 50\%$ of effects ^c on coronary outcomes in RCTs being statistically significant and consistent with expectation for dietary exposure in question, or significant association based on pooled analysis of clinical trials ^b
Excluded from causation score		
Specificity (7)	Specific exposure is related to only 1 disease; cautions that this criterion should not be overemphasized	Not evaluated in this review because CVD outcomes are highly intercorrelated and, consequently, associations between a single dietary exposure and multiple cardiovascular end points do not preclude a possible causal relationship; highly plausible that food would affect >1 form of CVD even when abnormalities have little relationship ^g
Plausibility (8)	An association that makes sense biologically is more likely to be causal; plausibility depends on biological knowledge of the day	Exposures selected in this review all meet plausibility criteria for credible scientific mechanism to explain associations
Analogy (9)	Weakest form of evidence of causality is arguing by analogy; largely reflects imagination or experience of the scientist	Not evaluated in this review because largely driven by creativity of the investigators and is the least convincing criterion

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction; RCT, randomized controlled trial; RR, relative risk.

^aRR cutoff points of no more than 0.83 and at least 1.20 to define a strong association were derived from the median values of the distribution of RR values in existing cohort studies for the beneficial and harmful dietary exposures, respectively.

^bAn association in the expected direction or consistent with expectation is simply an RR of less than 1.0 for beneficial dietary exposures and an RR of greater than 1.0 for harmful exposures.

^cPercentage values were calculated as the sum of all significant effects on primary outcomes divided by the total number of tests for an effect on primary outcomes multiplied by 100. If the percentage exceeded the prespecified cutoff value (eg, 50% for biological gradient), then the criterion was satisfied. The percentage cutoff values for these 2 criteria are summarized in the table.

^dCriterion 1 defines this association.

^eA modest association was defined as any statistically significant effect in the expected direction and no quantile showing a statistically significant effect in the opposite direction.

^fAlthough the measurement design of each cohort study is temporally correct, we retained this criterion in our guidelines to assess causality because temporality is necessary although not sufficient in itself to infer causation; thus, an absence of a temporal relationship between diet and coronary heart disease would preclude a causal link.

^gAnalysis of the results from RCTs is not meant to override the results from cohort studies, but rather to indicate whether the evidence from RCTs is concordant with that of cohort studies.

ues derived from the cohort studies and the sample size from all cohort studies pooled together for each particular dietary factor, with separate plots for beneficial and harmful dietary exposures. A slope of 0 would suggest that a propensity to study certain dietary factors more than others likely does not account for the variation in the effects across dietary ex-

posures. No associations were observed (supplementary appendix 3).

RESULTS

The **Figure** displays the number of studies evaluated and excluded through the stages of the literature

review. The search of the MEDLINE database yielded 146 prospective cohort studies describing 361 subcohorts and 43 RCTs involving 51 subgroups. Most of the cohort studies (125 [86%]) were primary prevention studies, whereas 32 RCTs (74%) were secondary prevention trials.

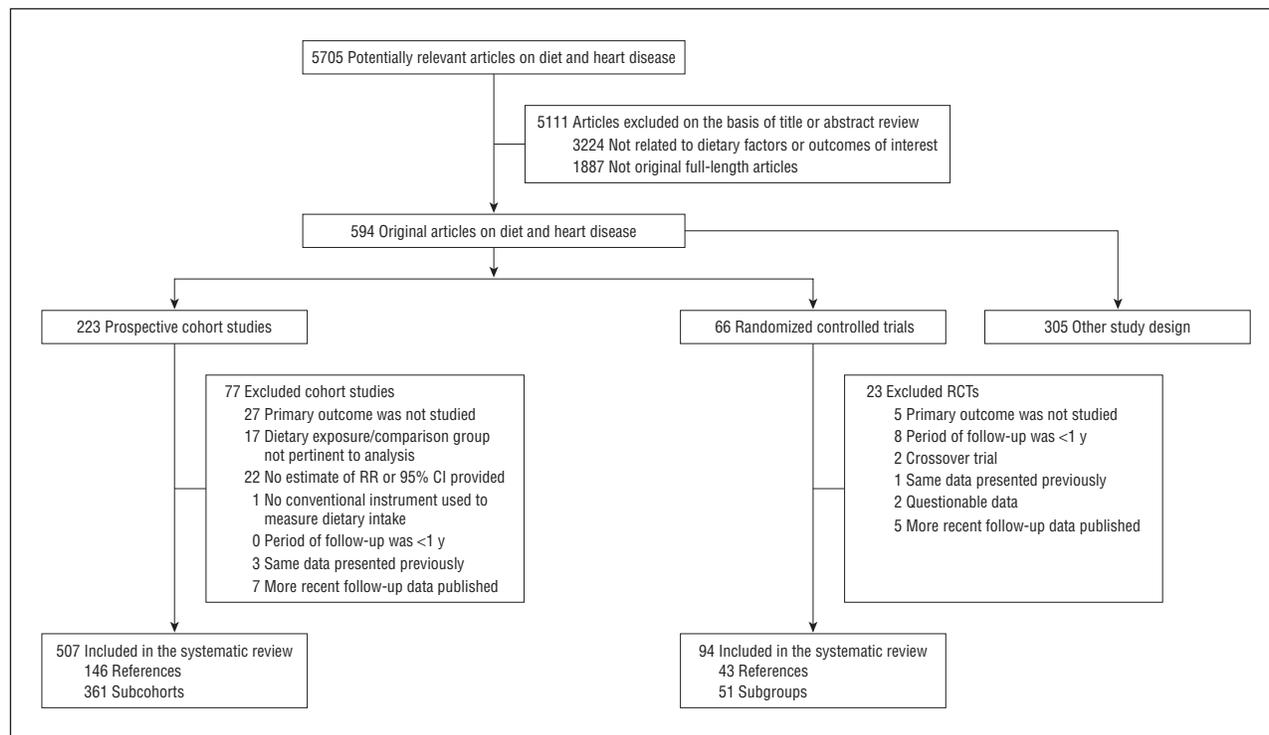


Figure. Flowchart summary of literature search. CI indicates confidence interval; RCT, randomized controlled trial; and RR, relative risk.

Supplementary appendix 4 summarizes the characteristics and results of the included prospective cohort studies by dietary exposure. Among the 361 subcohorts included in the review, 201 were from the United States, 130 were from Europe, and 12 were from Asia. For each dietary factor, an average of 29 209 individuals were included, and the median length of follow-up was 11 (range, 2.8-28) years; mean age was 53 years; and 41% were women. Most of the studies (89%) used a food frequency questionnaire to assess dietary intake.

Supplementary appendix 5 summarizes the characteristics and results of the included RCTs by dietary exposure. For each dietary variable, there was an average total of 7204 individuals, and the median length of follow-up was 3.7 (range, 1-12) years; mean age was 58 years; and 36% were women.

POOLED ESTIMATES FROM COHORT STUDIES

The pooled analyses of cohort studies showed that an increased consumption of alcohol (RR [95% CI] for heavy consumption, 0.69 [0.64-0.75]; for light/moderate consumption, 0.71

[0.67-0.75]), dietary beta carotene (0.73 [0.65-0.82]), fiber (0.78 [0.72-0.84]), fish (0.81 [0.70-0.92]), total folate (0.68 [CI, 0.57-0.79]), dietary folate (0.62 [0.50-0.79]), fruits (0.80 [0.66-0.93]), marine ω -3 fatty acids (0.86 [0.75-0.97]), monounsaturated fatty acids (0.80 [0.67-0.93]), nuts (0.70 [0.57-0.82]), vegetables (0.77 [0.68-0.87]), total vitamin C (0.82 [0.71-0.92]), dietary vitamin C (0.80 [0.68-0.91]), total vitamin E (0.77 [0.66-0.89]), dietary vitamin E (0.77 [0.55-0.99]), and whole grains (0.81 [0.75-0.86]) and increased Mediterranean (0.63 [0.53-0.72]) and high-quality diet patterns (0.63 [0.45-0.81]) were each associated with a significantly lower risk of CHD. Conversely, an increased consumption of *trans*-fatty acids (RR, 1.32 [95% CI, 1.16-1.48]) and foods with a high glycemic index (1.32 [1.10-1.54]) were associated with a significantly higher risk of CHD (**Table 2**).

Higher intake of α -linolenic acid, eggs, meat, milk, polyunsaturated fatty acids, saturated fatty acids, total fat, and ascorbic acid (vitamin C) and vitamin E supplements and prudent and western diet patterns were not significantly associated with CHD (Table 2). Among studies of higher methodologic quality, pru-

dent (RR, 0.73 [95% CI, 0.62-0.83]) and western (1.55 [1.27-1.83]) diet patterns were each associated with CHD. In keeping with previous information, fish intake was protective against fatal CHD (RR, 0.83 [95% CI, 0.71-0.94]), but marine ω -3 fatty acids (0.88 [0.66-1.11]) and α -linolenic acid (0.98 [0.60-1.36]) were not.

Table 3 shows the summary RRs for each dietary exposure, stratified by dietary assessment tool, sex, geographic region, and type of prevention strategy. Primary prevention studies indicate favorable associations for vitamin E, beta carotene, vitamin C, and fiber intake, whereas secondary prevention studies show beneficial associations for fish and ω -3 fatty acid intake. The intake of marine ω -3 fatty acids was beneficial in women. The summary estimates are generally consistent across the strata of other potential effect modifiers.

POOLED ESTIMATES FROM RCTs

The pooled analysis of RCTs showed that increased consumption of marine ω -3 fatty acids (RR, 0.77 [95% CI, 0.62-0.91]) and a Mediterranean dietary pat-

Table 2. Agreement of Observed Data From Cohort Studies With Bradford Hill Criteria for Assessing a Potential Causal Relationship Between Selected Dietary Exposures and Coronary Heart Disease^a

Dietary Exposure	Total No. of Patients	No. of Subcohorts	Strength, Summary RR (95% CI) ^b		Temporality ^b	Consistency in Coronary Outcomes, No. (%) ^b		Coherence ^b	No. of Criteria Met (of 4)
			Coronary Outcomes ^c	Coronary Outcomes and Secondary Events ^c		Coronary Risk or Mortality	Coronary Risk, Mortality, or MI		
"Mediterranean" diet ^d	66 337	4	0.63 (0.53-0.72) ^e	0.66 (0.57-0.75) ^e	Yes	4/4 (100) ^e	4/4 (100) ^e	Yes	4
High-quality diet	192 737	4	0.63 (0.45-0.81) ^e	0.63 (0.45-0.81) ^e	Yes	3/4 (75) ^e	3/4 (75) ^e	Yes	4
Vegetables	220 564	9	0.77 (0.68-0.87) ^e	0.77 (0.68-0.87) ^e	Yes	5/7 (71) ^e	6/11 (55)	Yes	4
Nuts	184 194	6	0.70 (0.57-0.82) ^e	0.67 (0.57-0.77) ^e	Yes	5/10 (50)	4/6 (67) ^e	Yes	4
Trans-fatty acids	145 132	4	1.32 (1.16-1.48) ^e	1.32 (1.16-1.48) ^e	Yes	3/4 (75) ^e	3/6 (50)	Yes	4
Glycemic index or load	338 410	8	1.32 (1.10-1.54) ^e	1.33 (1.13-1.52) ^e	Yes	4/6 (67) ^e	4/8 (50)	Yes	4
"Prudent" diet ^f	121 208	3	0.84 (0.61-1.07)	0.84 (0.61-1.07)	Yes	2/3 (67) ^e	2/3 (67) ^e	Yes	3 ^g
"Western" diet ^h	121 208	3	1.33 (0.86-1.79)	1.33 (0.86-1.79)	Yes	2/3 (67) ^e	2/3 (67) ^e	Yes	3 ^g
Monounsaturated fatty acids	101 521	4	0.80 (0.67-0.93) ^e	0.80 (0.67-0.93) ^e	Yes	2/4 (50)	3/5 (60)	Yes	3 ^g
Fish	363 228	29	0.81 (0.70-0.92) ^e	0.81 (0.71-0.92) ^e	Yes	8/36 (22)	11/48 (23)	Yes	3
Total folate	308 012	2	0.68 (0.57-0.79) ^e	0.68 (0.57-0.78) ^e	Yes	2/4 (50)	4/7 (57)	Yes	3
Dietary folate	104 307	4	0.62 (0.50-0.79) ^e	0.62 (0.50-0.79) ^e	Yes	0/1	2/4 (50)	Yes	3
Whole grains	356 070	11	0.81 (0.75-0.86) ^e	0.81 (0.75-0.86) ^e	Yes	3/11 (27)	5/13 (38)	Yes	3
Total vitamin E	509 739	5	0.77 (0.66-0.89) ^e	0.78 (0.66-0.89) ^e	Yes	6/16 (38)	6/17 (35)	Yes	3
Dietary vitamin E	183 206	8	0.77 (0.55-0.99) ^e	0.77 (0.55-0.99) ^e	Yes	2/8 (25)	2/8 (25)	Yes	3
Dietary beta carotene	138 741	10	0.73 (0.65-0.82) ^e	0.74 (0.65-0.82) ^e	Yes	4/9 (44)	5/10 (50)	Yes	3
Total vitamin C	595 376	5	0.82 (0.71-0.92) ^e	0.82 (0.72-0.92) ^e	Yes	6/19 (32)	6/20 (30.)	Yes	3
Dietary vitamin C	271 777	11	0.80 (0.68-0.91) ^e	0.80 (0.68-0.92) ^e	Yes	2/10 (20)	3/11 (27)	Yes	3
Alcohol, light/moderate consumption	1 747 107	70	0.71 (0.67-0.75) ^e	0.72 (0.68-0.76) ^e	Yes	27/69 (39)	31/82 (38)	Yes	3
Alcohol, heavy consumption	1 693 893	64	0.69 (0.64-0.75) ^e	0.70 (0.65-0.76) ^e	Yes	24/67 (36)	29/76 (38)	Yes	3
Fruits and vegetables	199 514	7	0.79 (0.72-0.87) ^e	0.79 (0.72-0.87) ^e	Yes	1/5 (20)	1/8 (12)	Yes	3
Fruits	222 706	10	0.80 (0.66-0.93) ^e	0.81 (0.68-0.94) ^e	Yes	1/7 (14)	2/11 (18)	Yes	3
Fiber	215 054	15	0.78 (0.72-0.84) ^e	0.78 (0.72-0.85) ^e	Yes	7/15 (47)	8/19 (42)	Yes	3
ω-3 Fatty acids									
Marine (excluding α-linolenic acid)	301 780	13	0.86 (0.75-0.97)	0.86 (0.75-0.97)	Yes	4/14 (29)	7/22 (32)	Yes	2 ⁱ
α-Linolenic acid	145 497	5	1.06 (0.92-1.20)	1.01 (0.84-1.18)	Yes	0/6	0/10	Yes	2
All	447 277	18	0.91 (0.81-1.00)	0.89 (0.80-0.99)	Yes	4/20 (20)	7/31 (23)	Yes	2
Supplementary vitamin E	162 244	4	0.83 (0.60-1.07)	0.83 (0.60-1.07)	Yes	2/4 (50)	2/4 (50)	Yes	2
Supplementary ascorbic acid	161 437	4	0.87 (0.60-1.13)	0.86 (0.61-1.11)	Yes	1/4 (25)	1/4 (25)	Yes	2
Total fat	126 439	7	0.99 (0.88-1.09)	0.99 (0.88-1.09)	Yes	1/9 (11)	1/9 (11)	Yes	2
Saturated fatty acids	160 673	11	1.06 (0.96-1.15)	1.06 (0.96-1.15)	Yes	4/12 (33)	4/14 (29)	Yes	2
Polyunsaturated fatty acids	102 937	6	1.02 (0.81-1.23)	1.02 (0.81-1.23)	Yes	1/6 (17)	1/8 (12)	Yes	2
Meat ^j	236 414	12	1.23 (0.98-1.49)	1.23 (0.98-1.49)	Yes	5/13 (38)	5/15 (33)	No	1
Eggs ^j	258 221	6	1.06 (0.89-1.23)	1.06 (0.89-1.23)	Yes	1/6 (17)	1/6 (17)	No	1
Milk ^k	216 820	8	0.94 (0.75-1.13)	0.91 (0.73-1.09)	Yes	1/8 (12)	1/8 (12)	No	1

Abbreviations: CI, confidence interval; MI, myocardial infarction; RR, relative risk.

^aThe characteristics and results of the cohort studies are presented in supplementary appendix 4 (available on request from the authors).

^bThe definition of each Bradford Hill criterion is shown in Table 1.

^cThe cohort studies typically report estimated intakes as quantiles (usually quartiles or quintiles). The higher intakes are compared with the lowest intakes and reported as odds ratios or RRs for each clinical outcome. We used these comparisons of extreme quantile groups across studies to compute summary estimates or, where incremental units are used, an increment equal to approximately 1 SD unit of intake.

^dThe "Mediterranean" dietary pattern emphasizes a higher intake of vegetables, legumes, fruits, nuts, whole grains, cheese or yogurt, fish, and monounsaturated relative to saturated fatty acids.

^eDenotes that the criterion for strength, consistency, or biological gradient is satisfied.

^fThe "prudent" dietary pattern is characterized by a high intake of vegetables, fruit, legumes, whole grains, and fish and other seafood.

^gBradford Hill score is 4 when restricting analyses to cohort studies of high methodologic quality (low risk of bias).

^hThe "western" pattern is characterized by a high intake of processed meat, red meat, butter, high-fat dairy products, eggs, and refined grains.

ⁱBradford Hill score is 3 when restricting analyses to cohort studies of high methodologic quality (low risk of bias).

^jIn an independent review of the literature by two of us (A.M. and L.D.), evidence of coherence was found for all of the dietary exposures except for meat, eggs, and milk.

^kWe could not differentiate between low vs high-fat milk intake because all of the studies except for one²⁰ did not measure the type of milk consumed (possibly because many of the cohorts in these studies originated in the 1970s when the consumption of reduced-fat milk was less common).

tern (0.32 [0.15-0.48]) were each associated with a significantly lower risk of CHD. Higher intake of beta carotene supplements, fiber, fish, folate supplements, fruits and vegetables, and poly-

unsaturated fatty acids relative to saturated fatty acids, total fat, and ascorbic acid and vitamin E supplements were not significantly associated with CHD. The summary RRs were gener-

ally consistent across the strata of methodologic quality (**Table 4**).

Cohort studies provide abundant evidence of an association with total mortality for many dietary

Table 3. Summary RRs and 95% CIs for the Association Between Each Dietary Exposure and Coronary Heart Disease in Cohort Studies, Stratified by Dietary Assessment Tool, Sex, Region, and Prevention Effort^a

Dietary Exposure	Dietary Assessment Tool ^b		Sex ^c			Region			Prevention Effort ^d	
	FFQ	Food Record	Men	Women	Both	United States	Europe	Asia	Primary	Secondary
"Mediterranean" diet ^e	0.66 (0.57-0.75)				0.66 (0.57-0.75)		0.67 (0.57-0.77)		0.64 (0.54-0.75)	0.69 (0.52-0.93)
High-quality diet	0.63 (0.45-0.81)			0.54 (0.45-0.63)		0.57 (0.45-0.70)	0.81 (0.09-1.54)		0.63 (0.45-0.81)	
Vegetables	0.83 (0.77-0.90)	0.52 (0.35-0.69)	0.79 (0.65-0.94)	0.81 (0.60-1.02)	0.68 (0.38-0.99)	0.71 (0.57-0.85)	0.85 (0.71-0.98)		0.77 (0.68-0.87)	
Nuts	0.67 (0.57-0.77)		0.76 (0.54-0.97)	0.72 (0.59-0.90)	0.60 (0.46-0.73)	0.66 (0.55-0.76)	0.87 (0.45-1.29)		0.67 (0.57-0.77)	
Trans-fatty acids	1.32 (1.16-1.48)		1.32 (1.09-1.56)	1.33 (1.07-1.66)		1.31 (0.87-1.75)	1.33 (1.13-1.52)		1.32 (1.16-1.48)	
Glycemic index or load	1.33 (1.13-1.52)		1.06 (0.91-1.20)	1.50 (1.29-1.71)		1.62 (1.21-2.03)	1.17 (1.01-1.33)		1.33 (1.13-1.52)	
"Prudent" diet ^f	0.84 (0.61-1.07)		0.70 (0.56-0.86) ^g	0.76 (0.60-0.98) ^g	1.06 (0.93-1.21) ^g	0.73 (0.62-0.83)	1.06 (0.93-1.21) ^g		0.84 (0.61-1.07)	
"Western" diet ^h	1.33 (0.86-1.79)		1.64 (1.24-2.17) ^g	1.46 (1.07-1.99) ^g	0.97 (0.85-1.10) ^g	1.55 (1.27-1.83)	0.97 (0.85-1.10) ^g		1.33 (0.86-1.79)	
Monounsaturated fatty acids	0.81 (0.68-0.93)		0.80 (0.62-0.98)	0.82 (0.62-1.10) ^g		0.81 (0.61-1.01)	0.80 (0.64-0.95)		0.80 (0.67-0.93)	
Fish	0.78 (0.66-0.90)	1.21 (0.18-2.24) ^g	0.85 (0.70-1.01)	0.77 (0.51-1.02)	0.78 (0.63-0.94)	0.80 (0.70-0.95)	0.87 (0.66-1.07)	0.74 (0.47-1.01)	0.83 (0.73-0.93)	0.45 (0.12-0.79)
Folate	0.72 (0.65-0.80)	0.54 (0.30-0.77)	0.54 (0.30-0.77)	0.75 (0.68-0.82)	0.57 (0.36-0.78)	0.75 (0.68-0.82)	0.54 (0.40-0.67)		0.69 (0.59-0.79)	0.61 (0.40-0.82)
Whole grains	0.80 (0.75-0.86)		0.80 (0.70-0.90)	0.78 (0.65-0.91)	0.82 (0.75-0.89)	0.80 (0.73-0.85)	0.86 (0.74-0.99)		0.81 (0.75-0.86)	
Vitamin E	0.78 (0.66-0.90)	0.75 (0.41-1.09) ^g	0.72 (0.63-0.81)	0.74 (0.56-0.93)	1.00 (0.76-1.24)	0.77 (0.65-0.88)	0.83 (0.50-1.15)		0.77 (0.65-0.88)	1.04 (0.58-1.51) ^g
Beta carotene	0.74 (0.64-0.83)	0.73 (0.53-0.93) ^g	0.75 (0.66-0.84)	0.78 (0.58-0.98)	0.55 (0.34-0.76)	0.76 (0.66-0.86)	0.70 (0.55-0.85)		0.72 (0.65-0.79)	1.34 (0.79-1.88) ^g
Vitamin C	0.85 (0.74-0.95)	0.80 (0.60-1.00) ^g	0.78 (0.64-0.92)	0.89 (0.74-1.03)	0.72 (0.35-1.08)	0.87 (0.74-1.00)	0.72 (0.56-0.89)		0.72 (0.68-0.86)	1.55 (0.98-2.12)
Alcohol, heavy consumption	0.69 (0.64-0.75)	1.02 (0.64-1.40) ^g	0.71 (0.64-0.79)	0.63 (0.54-0.71)	0.72 (0.52-0.93)	0.64 (0.59-0.70)	0.82 (0.68-0.97)	0.69 (0.32-1.06)	0.70 (0.63-0.76)	0.67 (0.58-0.77)
Alcohol, light/moderate consumption	0.72 (0.68-0.76)		0.72 (0.68-0.76)	0.72 (0.65-0.79)	0.69 (0.52-0.85)	0.71 (0.66-0.76)	0.73 (0.66-0.80)	0.66 (0.43-0.89)	0.70 (0.66-0.75)	0.72 (0.66-0.79)
Fruits and vegetables	0.79 (0.71-0.87)	0.81 (0.58-1.04) ^g	0.75 (0.58-0.92)	0.74 (0.50-0.99)	0.81 (0.72-0.90)	0.80 (0.73-0.88)	0.70 (0.41-0.99)		0.79 (0.72-0.87)	
Fruits	0.82 (0.67-0.98)	0.79 (0.49-1.08)	0.79 (0.49-1.09)	0.81 (0.53-1.09)	0.84 (0.68-1.00)	0.84 (0.69-0.99)	0.78 (0.53-1.04)		0.81 (0.68-0.94)	
Fiber	0.74 (0.65-0.83)	0.83 (0.62-1.04)	0.76 (0.68-0.84)	0.71 (0.57-0.84)	0.90 (0.76-1.03)	0.83 (0.78-0.87)	0.73 (0.57-0.88)		0.77 (0.70-0.84)	0.90 (0.65-1.15)
Total fat	1.04 (0.93-1.15)	1.04 (0.68-1.40)	0.95 (0.81-1.08)	1.05 (0.79-1.32)	1.04 (0.68-1.40)	0.91 (0.78-1.05)	1.08 (0.94-1.21)		0.98 (0.87-1.10)	1.04 (0.68-1.40)
Saturated fatty acids	1.10 (0.91-1.29)	1.04 (0.99-1.09)	1.03 (0.93-1.12)	1.17 (0.75-1.59)	1.73 (0.03-3.44)	1.06 (0.98-1.14)	1.07 (0.83-1.32)		1.06 (0.96-1.16)	1.01 (0.64-1.37) ^g
Polyunsaturated fatty acids	0.91 (0.64-1.18)	1.00 (0.66-1.34) ^g	1.12 (0.86-1.37)	0.75 (0.60-0.92) ^g	1.00 (0.66-1.34) ^e	0.98 (0.71-1.25)	1.13 (0.94-1.32)		1.03 (0.78-1.28)	1.06 (0.80-1.32)
ω-3 Fatty acids										
Marine (excluding α-linolenic acid)	0.86 (0.75-0.97)		0.97 (0.82-1.13)	0.70 (0.59-0.81)	0.88 (0.68-1.07)	0.83 (0.65-1.01)	0.99 (0.81-1.16)	0.74 (0.56-0.91)	0.88 (0.77-0.99)	0.69 (0.47-1.03) ^g
α-Linolenic acid	1.04 (0.86-1.21)	0.73 (0.25-1.22) ^g	1.12 (0.94-1.29)	0.90 (0.68-1.12) ^g	0.73 (0.25-1.22) ^g	0.92 (0.74-1.11)	1.08 (0.72-1.44)		1.04 (0.86-1.21)	0.73 (0.25-1.22) ^g
All	0.90 (0.80-0.99)	0.73 (0.25-1.22) ^g	1.01 (0.89-1.13)	0.74 (0.64-0.84)	0.87 (0.72-1.02)	0.85 (0.72-0.99)	1.02 (0.87-1.16)	0.74 (0.56-0.91)	0.91 (0.82-1.01)	0.70 (0.50-0.90)
Meat	1.23 (0.98-1.49)		1.65 (1.29-2.00)	1.22 (0.94-1.50)	0.92 (0.40-1.44)	1.32 (1.07-1.56)	0.92 (0.40-1.44)		1.20 (0.94-1.46)	1.71 (0.97-2.44)
Eggs	1.06 (0.89-1.23)		1.08 (0.79-1.48) ^g	0.91 (0.70-1.12)	1.21 (0.88-1.55)	1.00 (0.87-1.14)			1.06 (0.89-1.23)	
Milk	0.92 (0.69-1.15)	0.93 (0.64-1.22)	0.72 (0.55-0.89)	1.00 (0.71-1.30)	1.50 (0.81-2.19) ^g	1.05 (0.68-1.43)	0.83 (0.62-1.04)		0.91 (0.73-1.09)	

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; RR, relative risk.

^a Blank fields indicate that there were not enough studies available to compute summary RRs within the strata.

^b We did not compute RRs for cohort studies using 24-hour diet recall because there were only a handful of cohort studies using this dietary assessment tool (ie, for fish, whole grains, fiber, and folate), as shown in supplementary appendix 4 (available on request from the authors).

^c Each of the 3 sex columns contains studies that are not necessarily the same, and studies that present men and women together do not contribute to studies of men and women separately; therefore, the RRs for both are not the average of those for men and women pooled together.

^d Studies that included general or healthy populations were classified as primary prevention studies. Investigations that included subjects with coronary heart disease or a cardiovascular risk factor (eg, smoking, hypertension, or diabetes mellitus) were classified as secondary prevention studies.

^e The "Mediterranean" dietary pattern emphasizes a higher intake of vegetables, legumes, fruits, nuts, whole grains, cheese or yogurt, fish, and monounsaturated relative to saturated fatty acids.

^f The "prudent" dietary pattern is characterized by a high intake of vegetables, fruit, legumes, whole grains, and fish and other seafood.

^g Derived from only 1 study.

^h The "western" pattern is characterized by a high intake of processed meat, red meat, butter, high-fat dairy products, eggs, and refined grains.

Table 4. Evidence From RCTs^a

Dietary Exposure	Causation Score (of 4)	Total Trials		Trials With Low Risk of Bias, High Methodologic Quality		Consistent With Findings Using the Bradford Hill Criteria	Comments
		No. (%) of Tested Associations With Significant Effect ^b	Summary RR (95% CI)	No. (%) of Studies With Significant Effect	Summary RR (95% CI)		
"Mediterranean" diet ^c	4	2/2 (100) ^d	0.32 (0.15-0.48) ^d	...		Yes	Strong evidence of causation in cohort studies; strong effects in RCTs, albeit 1 study
Fish	3	0/3	1.12 (0.66-1.59)	...		No	Moderate evidence in cohort studies; no evidence of an effect in RCTs
Fruits and vegetables	3	0/2	1.01 (0.74-1.27)	...		Unknown	Unable to assess; only 1 RCT
Fiber	3	0/1	1.11 (0.96-1.29)	...		Unknown	Unable to assess; only 1 RCT
ω-3 Fatty acids							
Marine (excluding α-linolenic acid)	3	5/19 (26)	0.77 (0.62-0.91) ^d	1/9 (11)	0.57 (0.34-0.80) ^d	Yes	Moderate evidence in cohort studies; significant effect in RCTs
Marine and α-linolenic acid	2	5/20 (25)	0.80 (0.65-0.94) ^d	1/9 (11)	0.57 (0.34-0.80) ^d	No ^e	Weak evidence in cohort studies; significant effect in RCTs
Supplementary vitamin E	2	3/35 (9)	0.92 (0.84-1.01)	2/24 (8)	0.93 (0.82-1.03)	Yes	Weak evidence in cohort studies; nonsignificant effects in RCTs
Supplementary ascorbic acid	2	0/3	0.98 (0.70-1.25)	0/3	0.98 (0.70-1.25)	Yes	Weak evidence in cohort studies; nonsignificant effects in RCTs
Total fat	2	1/8 (12)	1.05 (0.99-1.11) ^f	0/3	1.01 (0.89-1.15) ^f	Yes	Weak evidence in cohort studies; no effect in RCTs
Saturated fatty acids ^g	2					Unknown	Unable to assess
Polyunsaturated fatty acids							
Excluding total fat interventions	2	1/12 (8)	0.94 (0.87-1.02)	1/7 (14)	0.95 (0.80-1.10)	Yes	Weak evidence in cohort studies; weak effect in RCTs
All studies	2	2/20 (10)	0.95 (0.91-0.99) ^d	1/10 (10)	0.97 (0.88-1.06)	Yes	Weak evidence in cohort studies; significant but weak effect in RCTs
Supplementary folate	Unknown	0/16	0.99 (0.91-1.06)	0/10	1.00 (0.92-1.08)	Unknown	Not studied in cohort studies; no effect in RCTs
Supplementary beta carotene	Unknown	1/14 (7)	1.01 (0.92-1.09)	1/14 (7)	1.01 (0.92-1.09)	Unknown	Not studied in cohort studies; nonsignificant effects in RCTs

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RR, relative risk; ellipses, no studies.

^aThe definition of experimental evidence from RCTs is shown in Table 1. No RCT data were available for high-quality, "prudent," and "western" diet patterns and intake of vegetables, nuts, *trans*-fatty acids, glycemic index or load, monounsaturated fatty acids, whole grains, dietary folate, dietary vitamins E and C, dietary beta carotene, alcohol, fruits, saturated fatty acids, meat, eggs, and milk. Thus, consistency with the Bradford Hill criteria is unknown.

^bIndicates the percentage of tested associations on coronary outcomes that show a significant effect, and consistent with expectation for the dietary exposure in question (see Table 1, criterion 6); therefore, the number of tested associations is often greater than the number of studies owing to assessment of multiple outcomes in some studies.

^cThe "Mediterranean" dietary pattern emphasizes a higher intake of vegetables, legumes, fruits, nuts, whole grains, cheese or yogurt, fish, and monounsaturated relative to saturated fatty acids.

^dDenotes that at least 50% of effects on coronary outcomes in RCTs are statistically significant and consistent with expectation for the dietary exposure in question, or a significant association based on pooled analysis of clinical trials.

^eCohort studies have assessed plant (α-linolenic acid) and marine (eicosapentaenoic acid and docosahexaenoic acid) sources of ω-3 fatty acids; RCTs have assessed predominantly marine sources.

^fHigh vs low total fat intake.

^gNo studies were available; this exposure was examined only in concert with other dietary changes.

exposures (supplementary appendix 6). Randomized controlled trials corroborate these associations for the consumption of ω-3 fatty acids and a Mediterranean diet because most of the other dietary factors have not been evaluated to date.

APPLICATION OF BRADFORD HILL GUIDELINES FOR CAUSALITY

Agreement of observed data from cohort studies with Bradford Hill criteria for each dietary exposure is pre-

sented in Table 2. Strong evidence supports a causal link with CHD (≥4 criteria) for several protective factors, including intake of vegetables and nuts and Mediterranean and high-quality dietary patterns, and for harmful factors, including consump-

Table 5. Summary of the Evidence of a Causal Association Between Diet and Coronary Heart Disease, as Determined From Examination of Prospective Cohort Studies Using the Bradford Hill Guidelines and Consistency With Findings From RCTs^a

Evidence of a Causal Association From Cohort Studies	Cohort Data Only	Supported by RCTs
Strong		
"Mediterranean" diet ^b		Yes
High-quality diet	✓	
Vegetables	✓	
Nuts	✓	
<i>Trans</i> -fatty acids	✓	
Glycemic index or load	✓	
"Prudent" diet ^{c,d}	✓	
"Western" diet ^{d,e}	✓	
Monounsaturated fatty acids ^d	✓	
Moderate		
Fish		No
Marine ω-3 fatty acids		Yes
Dietary folate	✓	
Supplementary folate		RCT data only
Whole grains	✓	
Dietary vitamin E	✓	
Dietary beta carotene	✓	
Supplementary beta carotene		RCT data only
Dietary vitamin C	✓	
Alcohol, light/moderate consumption	✓	
Alcohol, heavy consumption	✓	
Fruits	✓	
Fiber	✓	
Weak		
Supplementary vitamin E		Yes
Supplementary ascorbic acid		Yes
Total fat		Yes
Saturated fatty acids	✓	
Polyunsaturated fatty acids		Yes
ω-3 Fatty acids, total		No ^f
Meat	✓	
Eggs	✓	
Milk	✓	

Abbreviation: RCT, randomized controlled trial.

^aThe analysis of the results from RCTs is not meant to override the results from cohort studies, but rather to indicate whether the evidence from RCTs is concordant with that of cohort studies.

^bThe "Mediterranean" dietary pattern emphasizes a higher intake of vegetables, legumes, fruits, nuts, whole grains, cheese or yogurt, fish, and monounsaturated relative to saturated fatty acids.

^cThe "prudent" dietary pattern is characterized by a high intake of vegetables, fruit, legumes, whole grains, and fish and other seafood

^dStrong evidence was found when we restricted analyses to cohort studies of high methodologic quality (low risk of bias).

^eThe "western" pattern is characterized by a high intake of processed meat, red meat, butter, high-fat dairy products, eggs, and refined grains.

^fCohort studies have assessed plant (α-linolenic acid) and marine (eicosapentaenoic acid and docosahexaenoic acid) sources of ω-3 fatty acids; RCTs have assessed predominantly marine sources.

tion of *trans*-fatty acids and foods with a high glycemic index or load. There is also strong evidence supporting a valid association for monounsaturated fatty acid intake and a prudent diet (protective factors) as well as a western diet (harmful factor) among studies of high methodologic quality. Moderate evidence (3 criteria) for associations exists for intake of fish, marine ω-3 fatty acids, folate, whole grains, dietary vitamins E and C, beta caro-

tene, alcohol, fruit, and fiber. Weak evidence (≤2 criteria) is present for protective factors, including intake of supplementary vitamin E and ascorbic acid, polyunsaturated fatty acids, α-linolenic acid, eggs, and milk, and for harmful factors, including intake of meat, saturated fatty acids, and total fat. In separate analyses of the biological gradient (supplementary appendix 7), evidence of a linear dose-response with CHD is found for most of the di-

etary exposures except for mono-unsaturated fatty acids and total fat, folate, fruits, ω-3 fatty acids, fish, vitamin C, eggs, and milk.

As shown in Table 4, sufficient support from RCTs to satisfy the criterion for experimental evidence is observed only for marine or total ω-3 fatty acid intake and a Mediterranean dietary pattern. Little or weak evidence from RCTs is found for consumption of fruits, vegetables, fish, fiber, polyunsaturated fatty acids, and total fat and supplemental intake of beta carotene, vitamin E, ascorbic acid, and folate. Other factors have not been evaluated singly in clinical trials (Table 4). The evidence from RCTs agrees with the Bradford Hill results from cohort studies for intake of ascorbic acid and vitamin E supplements, polyunsaturated fatty acids, and total fats and a Mediterranean dietary pattern, but disagree for fish consumption, which shows moderate evidence of a causal link with CHD in cohort studies but virtually no effect in RCTs. Among the factors with strong evidence of causation, only overall healthy dietary patterns are significantly associated with CHD in RCTs (**Table 5**).

COMMENT

This review is, to our knowledge, the first to systematically assess whether a valid association exists between dietary exposures and CHD using the Bradford Hill guidelines. In applying a predefined algorithm, we identified strong evidence of a causal relationship for protective factors, including intake of vegetables, nuts, and monounsaturated fatty acids and Mediterranean, prudent, and high-quality dietary patterns, and harmful factors, including intake of *trans*-fatty acids and foods with a high glycemic index or load and a western dietary pattern. Among these dietary exposures, however, only a Mediterranean dietary pattern has been studied in RCTs and significantly associated with CHD. In addition, we found modest evidence to support a causal relationship for intake of fish, marine ω-3 fatty acids, folate, whole grains, dietary vitamins E and C and beta carotene, alcohol, fruits, and fiber, and weak evi-

dence of causation for intake of supplementary vitamin E and ascorbic acid, saturated and polyunsaturated fatty acids and total fat, α -linolenic acid, meat, eggs, and milk. The modest or weak evidence of these dietary exposures is mostly consistent with the findings of RCTs, although RCTs have yet to be conducted for several factors. Taken together, these findings support a causal relationship between only a few dietary exposures and CHD, whereas the evidence for most individual nutrients or foods is too modest to be conclusive.

A wealth of epidemiologic studies have evaluated associations between dietary exposures and CHD. The general consensus from the evidence currently available is that a reduced consumption of saturated and *trans*-fatty acids and a higher intake of fruits and vegetables, polyunsaturated fatty acids including ω -3 fatty acids, and whole grains are likely beneficial.²¹⁻²³ This is reflected in the revised Dietary Guidelines for Americans 2005 from the US Departments of Health and Human Services and Agriculture.²⁴ However, little direct evidence from RCTs supports these recommendations. In some cases, RCTs have not been conducted, and RCTs that have been conducted have generally not been adequately powered or have evaluated surrogate end points rather than clinical outcomes. Despite this lack of information, evidence-based recommendations derived from cohort studies have been advocated.²⁵ This is cause for concern because dietary advice to limit the intake of a certain nutrient (ie, dietary fat) may result in increased consumption of another (ie, carbohydrates), which can have adverse effects on CHD risk factors.²⁶ Moreover, without large prospective studies in which multiple health outcomes are evaluated, recommendations to modify a dietary component may decrease the likelihood of one chronic disease (ie, CHD) at the cost of increasing another (ie, cancer).¹⁶

We found strong evidence that *trans*-fatty acids are associated with CHD risk, but weak evidence implicating saturated and polyunsaturated fatty acids and total fat intake. Relatively few cohort studies have shown that a higher intake of poly-

unsaturated fatty acids or a lower intake of saturated fatty acids is related to a reduced risk of CHD.²⁷ Ecological data from the Seven Countries Study showed a strong positive association ($r=0.73$) between saturated fatty acid intake and CHD incidence,¹ although a much lower correlation was observed for total fat ($r=0.39$), suggesting that not all types of fat (ie, polyunsaturated fatty acids) are associated with an increased CHD risk. However, these data were interpreted by some to mean that all fats are associated with increased CHD risk, and subsequent dietary guidelines advocated low-fat diets.²¹⁻²³ More recently, the lack of benefit of diets of reduced total fat has been established,²⁸ and the evidence supporting the adverse effect of *trans*-fatty acids on cholesterol levels²⁹ and CHD³⁰⁻³⁴ has increased, which is reflected in our findings. Single-nutrient RCTs have yet to evaluate whether reducing saturated fatty acid intake lowers the risk of CHD events. For polyunsaturated fatty acid intake, most of the RCTs have not been adequately powered and did not find a significant reduction in CHD outcomes. On the other hand, mechanistic studies have demonstrated that diets low in total fat are associated with increased triglyceride and lower high-density lipoprotein cholesterol levels, whereas diets enriched with unsaturated fatty acids such as olive oil have positive effects on serum lipids.²⁹ Further work is needed to demonstrate the beneficial effects of these fatty acids on clinical outcomes.

Our results support an association between foods with higher glycemic index values and CHD outcomes. Metabolic studies have shown that higher glycemic index scores are associated with coronary risk factors, such as higher fasting triglycerides and lower high-density lipoprotein cholesterol levels.³⁵ Our findings, however, do not imply that every food with a low glycemic index is equally beneficial. Nevertheless, the glycemic index represents 1 functional property of food that can help guide dietary choices and may effectively organize a healthy dietary pattern, if used carefully. This functional index may be supplemented with information about glycemic load, which

reflects weighted carbohydrate intake and may provide further information about food choices based on appropriate serving size.

We found moderate evidence of valid associations involving fish intake and heterogeneity in the effects of ω -3 fatty acids. Metabolic studies have shown that these factors exert beneficial effects on surrogate measures of CHD such as levels of serum triglycerides and thrombotic factors, markers of endothelial dysfunction, and prevention of cardiac arrhythmias.^{36,37} The findings from cohort studies, however, have been inconsistent, and some have reported a detrimental effect.^{31,32,38,39} Our summary estimate (RR, 0.81) for fish intake and CHD risk was similar to that reported in a meta-analysis by Whelton et al,⁴⁰ who also reported similar estimates for fatal vs nonfatal CHD. A previous systematic review reported a stronger protective effect for fish intake in populations at higher risk of CHD than initially healthy populations,⁴¹ which we also observed. Similarly, our analysis showed that the effects of marine ω -3 fatty acids on CHD events are context driven because benefits are observed predominantly in female cohorts and secondary prevention studies, and the individual RCTs corroborated these benefits in subjects with CHD. However, a meta-analysis by Bucher et al⁴² suggested that an equal benefit from dietary and supplemental sources existed. Our findings did not support an association between intake of plant ω -3 fatty acids (eg, α -linolenic acid) and CHD in cohort studies, and evidence from RCTs is still lacking. These findings are consistent with recent information showing that α -linolenic acid supplementation does not affect cardiovascular risk markers.⁴³ Collectively, the evidence suggests a benefit of increased marine ω -3 fatty-acid intake against CHD in certain population subsets, although more studies are needed before widespread recommendations are made for the general population.

The discrepant findings of cohort studies vs RCTs often draw the attention of investigators. For instance, high-impact clinical trials such as Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Mio-

cardio, Heart Outcomes Prevention Evaluation, Heart Outcomes Prevention Evaluation—The Ongoing Outcomes, and the Physician's Health Study^{3,7,13,44} did not support the findings of large cohort studies that supported a protective association between vitamin E and beta carotene intake and CHD. In our analysis, differentiating between dietary and supplemental intake and implementation of the Bradford Hill guidelines helped to demonstrate that discrepant results involving the 2 designs are minimal. In particular, our findings of modest or weak evidence of a causal link between CHD and intake of polyunsaturated fatty acids and total fat and vitamin E and ascorbic acid supplements are compatible with the results from RCTs. Similarly, the strong evidence of causation involving a Mediterranean dietary pattern is compatible with the evidence from the Lyon Diet Heart Study trial. These findings lend support to the usefulness of the Bradford Hill guidelines in gauging the evidence of causation and emphasize the importance of examining the evidence from observational studies, given some of the limitations of RCTs (eg, subject compliance, disease latency, and duration of exposure).

We observed strong evidence of a causal link between CHD and dietary patterns. Population-based cohort studies have demonstrated the protective effect of a quality diet against CHD and all-cause mortality,⁴⁵⁻⁴⁹ and these benefits are additive with other lifestyle activities aimed at improving health.⁴⁷ The Lyon Diet Heart Study showed that a Mediterranean dietary pattern reduces cause-specific and all-cause mortality in patients with CHD.⁵⁰ Dietary patterns have the advantage of taking into account the complex interactions and cumulative effects of multiple nutrients within the entire diet because these effects may be larger and easier to detect than the effect of a single nutrient or food.^{51,52} Finally, CHD is a complex condition involving numerous physiologic systems, which makes it unlikely that modifying the intake of a few nutrients would alter these systems and influence clinical outcomes. Given the advantages of evaluating dietary patterns vs single nutrient components, we recommend that

future RCTs test various dietary patterns in sufficiently large populations and determine the effects of these patterns on multiple important health outcomes, including cardiovascular disease and cancer.

Our study has a number of strengths because we undertook several measures to minimize bias, including restricting our review to studies with the strongest causal inference (eg, cohort studies and RCTs), conducting an independent assessment of study eligibility by 2 of the authors, using predefined criteria to evaluate the evidence of causation, and performing stratification analyses for a number of extraneous variables. In addition, we examined high-quality or larger studies with sufficient outcome events, evaluated the potential for heterogeneity of effects across cohort studies, and assessed publication bias.

We may be criticized for creating arbitrary definitions of strong, moderate, and weak evidence, although these classifications have face validity and similar scoring systems have been used to assess the evidence of causation from observational studies.^{53,54} Second, we had to derive the RR cutoff points to define a strong association from the distribution of RR values in cohort studies because the true cutoff points for defining clinically meaningful effects are not known. Third, the heterogeneity of cohort studies may have influenced our results. However, our scatterplots of RR values against the difference in mean and median intake between quantile extremes showed no relationship for each dietary predictor, suggesting that differences in mean intake across studies do not explain the variation in RR values. Last, the evidence of causation may depend on the prevention strategy (primary vs secondary) or dietary assessment tool used in studies or may vary across populations. However, our subanalysis showed that, in general, the summary estimates are consistent across the strata of potential effect modifiers.

CONCLUSIONS

Our implementation of the Bradford Hill criteria identified strong evidence that a causal association ex-

ists between CHD and intake of vegetables, nuts, monounsaturated fatty acids, foods with a high glycemic index, *trans*-fatty acids, and overall diet quality or dietary patterns. Among these factors, only a Mediterranean dietary pattern was related to CHD in RCTs. Although investigations of dietary components may help to shed light on mechanisms behind the benefits of dietary patterns, it is unlikely that modifying the intake of a few nutrients or foods would substantially influence coronary outcomes. Our findings support the strategy of investigating dietary patterns in cohort studies and RCTs for common and complex chronic diseases such as CHD.

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REFERENCES

- Keys AB, Aravanis C. *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease*. Cambridge, MA: Harvard University Press; 1980.
- Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994; 330(15):1029-1035.
- Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334(18):1145-1149.
- Rapola JM, Virtamo J, Ripatti S, et al. Randomised trial of alpha-tocopherol and beta-carotene supplements on incidence of major coronary events in men with previous myocardial infarction. *Lancet*. 1997; 349(9067):1715-1720.
- Virtamo J, Rapola JM, Ripatti S, et al. Effect of vitamin E and beta carotene on the incidence of primary nonfatal myocardial infarction and fatal coronary heart disease. *Arch Intern Med*. 1998;158(6):668-675.
- Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst*. 1999; 91(24):2102-2106.
- Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P; Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342(3):154-160.
- Ness AR, Smith GD, Hart C. Milk, coronary heart disease and mortality. *J Epidemiol Community Health*. 2001;55(6):379-382.
- de Gaetano G; Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet*. 2001;357(9250): 89-95.
- Lonn E, Yusuf S, Hoogwerf B, et al; HOPE Study; MICRO-HOPE Study. Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: results of the HOPE Study and MICRO-HOPE substudy. *Diabetes Care*. 2002;25(11):1919-1927.
- Hodis HN, Mack WJ, LaBree L, et al; VEAPS Research Group. Alpha-tocopherol supplementation in healthy individuals reduces low-density lipoprotein oxidation but not atherosclerosis: the Vitamin E Atherosclerosis Prevention Study (VEAPS). *Circulation*. 2002;106(12):1453-1459.
- Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005;294(1): 56-65.
- Lonn E, Bosch J, Yusuf S, et al; HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA*. 2005;293(11):1338-1347.
- Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295-300.
- Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1998.
- Woolf SH. Weighing the evidence to formulate dietary guidelines. *J Am Coll Nutr*. 2006;25(3)(suppl):277S-284S.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996; 17(1):1-12.
- Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med*. 2001;135(11):982-989.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
- Hu FB, Stampfer MJ, Manson JE, et al. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. *Am J Clin Nutr*. 1999;70(6):1001-1008.
- American Heart Association Nutrition Committee; Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006; 114(1):82-96.
- Pyörälä K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice: recommendations of the task force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Atherosclerosis*. 1994; 110(2):121-161.
- Pyörälä K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice: recommendations of the task force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Eur Heart J*. 1994;15(10): 1300-1331.
- US Department of Health and Human Services; US Department of Agriculture. Dietary guidelines for Americans 2005. <http://www.healthier.us.gov/dietaryguidelines>. Accessed April 7, 2008.
- Srinath Reddy K, Katan MB. Diet, nutrition and the prevention of hypertension and cardiovascular diseases. *Public Health Nutr*. 2004;7(1A):167-186.
- Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med*. 2003;348(21):2074-2081.
- Hu FB, Stampfer MJ, Rimm EB, et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA*. 1999; 281(15):1387-1394.
- Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006; 295(6):655-666.
- Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N Engl J Med*. 1990;323(7):439-445.
- Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. *Am J Epidemiol*. 2005; 161(7):672-679.
- Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *BMJ*. 1996; 313(7049):84-90.
- Pietinen P, Ascherio A, Korhonen P, et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol*. 1997;145(10):876-887.
- Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med*. 1997;337(21):1491-1499.
- Oomen CM, Ocke MC, Feskens EJ, van Erp-Baart MA, Kok FJ, Kromhout D. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet*. 2001;357(9258):746-751.
- Jeppesen J, Schaaf P, Jones C, Zhou MY, Chen YD, Reaven GM. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. *Am J Clin Nutr*. 1997;65(4):1027-1033.
- Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids: recent studies. *Circulation*. 1996;94(7):1774-1780.
- Connor SL, Connor WE. Are fish oils beneficial in the prevention and treatment of coronary artery disease? *Am J Clin Nutr*. 1997;66(4)(suppl):1020S-1031S.
- Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med*. 1995;332(15):977-982.
- Oomen CM, Ocke MC, Feskens EJ, Kok FJ, Kromhout D. Alpha-linolenic acid intake is not beneficially associated with 10-y risk of coronary artery disease incidence: the Zutphen Elderly Study. *Am J Clin Nutr*. 2001;74(4):457-463.
- Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. *Am J Cardiol*. 2004; 93(9):1119-1123.
- Marckmann P, Gronbaek M. Fish consumption and coronary heart disease mortality: a systematic review of prospective cohort studies. *Eur J Clin Nutr*. 1999;53(8):585-590.
- Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2002;112(4):298-304.
- Wendland E, Farmer A, Glasziou P, Neil A. Effect of alpha linolenic acid on cardiovascular risk markers: a systematic review. *Heart*. 2006;92(2): 166-169.
- Gruppo Italiano per lo Studio della Sopravvivenza Nell'Infarto Miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione Trial. *Lancet*. 1999;354(9177): 447-455.
- Kant AK, Schatzkin A, Graubard BI, Schairer C. A prospective study of diet quality and mortality in women. *JAMA*. 2000;283(16):2109-2115.
- Trichopoulos D, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*. 2003; 348(26):2599-2608.
- Knoops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE Project. *JAMA*. 2004;292(12):1433-1439.
- Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. *Am J Clin Nutr*. 2000;72(4):912-921.
- Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB. Dietary patterns and the risk of coronary heart disease in women. *Arch Intern Med*. 2001; 161(15):1857-1862.
- de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet*. 1994;343(8911):1454-1459.
- Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002; 13(1):3-9.
- Kant AK. Dietary patterns and health outcomes. *J Am Diet Assoc*. 2004;104(4):615-635.
- Holt RI, Peveler RC. Antipsychotic drugs and diabetes: an application of the Austin Bradford Hill criteria. *Diabetologia*. 2006;49(7):1467-1476.
- DiFranza JR, Wellman RJ, Sargent JD, Weitzman M, Hipple BJ, Winickoff JP; Tobacco Consortium, Center for Child Health Research of the American Academy of Pediatrics. Tobacco promotion and the initiation of tobacco use: assessing the evidence for causality. *Pediatrics*. 2006;117(6):e1237-e1248.