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Empirical evaluation of meta-analytic approaches for nutrient and health outcome dose-response data

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Abstract

The objective of this study is to empirically compare alternative meta-analytic methods for combining dose-response data from epidemiological studies. We identified meta-analyses of epidemiological studies that analyzed the association between a single nutrient and a dichotomous outcome. For each topic, we performed meta-analyses of odds ratios with five approaches: using extreme exposure categories only, two-step approach (first calculated study-specific effects then combined across studies) using unadjusted data, two-step approach using adjusted data, one-step approach (analyzed all data in one regression model) using unadjusted data, and one-step approach using adjusted data. Meta-analyses including only extreme exposure categories gave consistently bigger effects and wider confidence intervals than meta-analyses using all data. Confidence intervals of effect sizes were generally wider in meta-analyses with the two-step approach, compared with the one-step approach. Meta-analyses using unadjusted data and adjusted data differed, with no consistent pattern of discordance in direction, statistical significance, or magnitude of effect. We discourage using meta-analysis approaches that only use data from extreme exposure categories. The one step approach generally has higher precision than the two-step approach. Sensitivity analysis comparing results between meta-analyses of adjusted and unadjusted data may be useful in indicating the presence of confounding.

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Supporting information may be found in the online version of this article.

Keywords

meta-analysis; dose-response data; evidence-based methodology; epidemiological data

1. Introduction

Dose-response relationships are often assessed when evaluating epidemiological data related to diet and health outcomes. For instance, the risk of mortality from lung cancer increases with increasing tar level and number of cigarettes smoked per day (Harris *et al.*, 2004); the risk of coronary heart disease decreases as the amount of dietary fiber increases (Bazzano *et al.*, 2002). Results are often reported by categories of exposure, as a relative risk or odds ratio and its confidence interval compared with a common reference group. These effect estimates are often adjusted for covariates and are reported with the unadjusted number of cases and controls for each exposure level.

Here, we focus on the meta-analysis of studies that model the probability of an event (e.g., lung cancer or coronary heart disease) as a function of ordered categories of exposure (e.g., percentiles or other categorizations of nutrient intake) with or without adjustments for other factors, most often by using logistic regression models. The regression coefficients for each nutrient intake category represent the odds ratio (OR) for experiencing an event within the nutrient intake category, versus the reference category, adjusted for other predictors. A major challenge in the meta-analysis of such data is that there is not one but $K-1$ effect sizes from each study (where K is the number of nutrient exposure categories), which are correlated because they share the common reference category

To address this challenge, many applied meta-analyses simply synthesize the effect size of the extreme exposure categories. This is wasteful of data because it ignores information on other exposure categories and introduces heterogeneity because, across studies, the difference in the mean exposures in the extreme categories can be highly variable. More nuanced methods improve upon these shortcomings. One group of methods makes use of a two-step approach: the first step estimates a (linear) dose-response relationship in each study by using the $K-1$ effect sizes and accounting for their correlation; the second step combines these slopes across studies (DuMouchel, 1995; Greenland and Longnecker, 1992; Smith *et al.*, 1995; Tweedie and Mengersen, 1995). Another group of methods combines all data in a single estimation step. For example, Berlin *et al.* (1993) approximate the within study covariance of the correlated effect sizes with multivariate normal distributions and combine all data in a weighted linear regression, whereas Cook *et al.* (2001) use a discrete (multinomial) likelihood.

In the more nuanced methods, the correlations between the $K-1$ effect sizes are incorporated in the analyses. The back-calculations of correlations for the $K-1$ effect sizes is based on recovering the counts in the $2 \times K$ cross-classification of events and no events versus the K categories of exposure by solving a system of equations. As discussed by Orsini *et al.* (2012), Greenland and Longnecker (1992) use unadjusted effect sizes to recover the actual counts in the $2 \times K$ table, whereas Hamling *et al.* (2008) use effects adjusted for confounders to recover 'effective counts', which can be used to recreate the adjusted effects and their

variances and covariances. Orsini (2012) note that the two methods can differ substantially when the adjusted and crude effect sizes and confidence intervals are dissimilar and provide software for implementing both.

The aim of this empirical study was to compare the point estimates and confidence intervals for dose-response associations using different statistical techniques for conducting meta-analysis in a systematically assembled database of nutrient-outcome associations. Because the true associations are not known, this study cannot assess the validity of the evaluated methods. It can however describe the (dis)similarity of their findings. Specifically, we compared point estimates and confidence intervals between (1) meta-analyses using only data from extreme exposure categories versus meta-analyses using data from all exposure categories, (2) meta-analyses using observed (crude, unadjusted) count data versus estimates obtained from adjusted data, and (3) meta-analyses using the two-step approach, where study-specific effect sizes are first calculated and then combined across studies, versus the one-step approach, where data from all primary studies are analyzed in one regression model.

2. Methods

2.1. Selection of observational studies with dose-response data

From a previous study, we developed a database of published meta-analyses of micronutrient topics by systematically searching electronic literature databases (Chung et al., 2009a, 2009b). We identified 142 systematic reviews linking micronutrients and health outcomes. We performed an updated literature search to identify systematic reviews published between July 2007 (our last search date) and April 2009. The search strategy is shown in Supplemental Table 1. Eligible meta-analyses met the following criteria: systematic review with meta-analysis, included more than one observational study, analyzed a single nutrient and health outcome association, analyzed a nutrient that does not provide energy, and reported a dichotomous outcome. Of note, the primary goal of the dataset development was to identify topics of nutrition and health associations from systematic reviews for which published data from individual studies were available in the peer reviewed literature. The goal was not to obtain a comprehensive list of systematic reviews of all micronutrient topics.

The full-text publications of the eligible reviews in the database were retrieved and reviewed to identify eligible observational studies. Eligible observational studies must have met the following inclusion criteria: included in the published meta-analyses, analyzed a single nutrient and health outcome association, reported both unadjusted data and adjusted effect sizes, and reported the nutrient intake per exposure category. Full-text publications of the eligible observational studies were retrieved. Of note, the goal was to compare the point estimates and confidence intervals with the alternative methods in a sample of observational studies, not to assess the effects of specific nutrient-health outcome association (topic). Therefore, the completeness of primary studies within each nutrition topic was not relevant to this work.

2.2. Data collection

Data extracted from each primary study included nutrient-outcome association evaluated, number of events and number of participants per exposure category, exposure categorization and mean or median intakes per exposure category, adjusted effect size, and its 95% confidence interval. When mean or median intake was not reported, we used the midpoint of the range of intake. When the lower or upper limit of the intake range was not reported (in the lowest or highest intake categories), we arbitrarily set the mean intake of the lowest intake category as 80% of the lower cutoff of the second lowest intake category, and the mean intake of the highest intake category as 120% of the higher cutoff of the second highest intake category. Meta-analytic calculations of dose response relationships can be sensitive to the choice of the mean intakes in each exposure interval (Berlin *et al.*, 1993; Hartemink *et al.*, 2006; Il'yasova *et al.*, 2005; Shi and Copas, 2004). Further, for highly skewed intakes, the mean of the upper intake category can be higher than the herein imputed value. We did not conduct any sensitivity analyses in this empirical evaluation but describe approaches advocated in the literature in the discussion section.

2.3. Statistical analyses

For each study, we calculated the 'effective numbers' of events and participants for each exposure category using methods described by Hamling (2008). Briefly, we used the adjusted effect sizes (log odds ratios from case-control studies, log rate ratios from cohort studies), their variances (95% confidence intervals or standard error), and observed (crude, unadjusted) count data to recover the effective numbers by solving sets of linear and nonlinear equations (different equations are used for log odds ratios and log rate ratios). The resulting effective numbers incorporate the effect of covariate adjustments to the crude count data. The result of a logistic regression (for case control studies) or a Poisson regression (for cohort studies) performed on the effective numbers without covariate adjustments is similar to the result of logistic or Poisson regression with covariate adjustment but using the observed count data. Because the effective numbers for the person-years of exposure were large, a logistic and a Poisson regression yielded numerically similar results. With large samples, the Poisson approximates the binomial distribution. Based on this fact, after obtaining the effective numbers, we used only logistic models for dose-response meta-analysis. We effectively use log ORs as the metric of choice.

For each nutrition topic, meta-analyses of log ORs were conducted with five approaches: (1) meta-analysis using only log OR between the extreme exposure categories, (2) meta-analysis with the two-step approach, using observed (crude, unadjusted) count data, (3) meta-analysis with the two-step approach, using effective numbers, (4) meta-analysis with the one-step approach, using observed count data, and (5) meta-analysis with the one-step approach, using effective numbers. Both homogeneous ('fixed') effect and random-effects meta-analyses were conducted for each of the five approaches, so that a total of ten models were performed for each nutrition topic. The analyses described below assume linear dose response.

- i. For meta-analysis of log ORs using only the extreme exposure categories, we used inverse variance synthesis to calculate the summary log OR. For random effects

analyses, we estimated between-study heterogeneity with the estimator of DerSimonian and Laird (1986).

- ii. We estimated the dose response slope, that is the log relative OR per unit change in exposure dosage in each study from a logistic regression on a dataset created using the observed count data (number of events and participants at risk) and assuming that participants in the same exposure category had the mean exposure dosage intake. We combined these unadjusted dose-response slopes with fixed and random effects meta-analysis, as per (1) earlier.
- iii. We repeated the analysis in (2) by using a dataset created with the effective numbers that incorporates the effects of covariate adjustments.
- iv. For meta-analysis with the one-step approach, we created a synthetic participant-level dataset by using the observed count data (number of events and participants at risk) from each study, assuming that participants in the same exposure category had the mean exposure dosage intake. By using this dataset, we performed logistic regression with a fixed effect, β , for exposure and fixed effects, α_k , for each study such that

$$\text{logit}(\pi_{ij}) = a_i + \beta \text{dose}_{ij}, \quad (1)$$

where dose_{ij} is the mean exposure for the dosage category of the j th exposure category in study i and a_i study level fixed intercepts. The summary dose-response slope is then just β . The random effects version of ([1]) assumes random slopes β_i across studies

$$\text{logit}(\pi_{ij}) = a_i + \beta_i \text{dose}_{ij}, \quad (2)$$

which are normally distributed around the mean (summary) dose response slope β with heterogeneity τ_β^2 .

- v. We repeated the analyses in (4) by using a dataset created with the effective numbers that incorporates the effects of covariate adjustments.

The first step in (2) and (3) and the models in (4) and (5) were fitted with maximum likelihood in the generalized linear model framework. Exponents of summary estimates obtained from the described methods were used to obtain ORs. Within each nutrition topic, we compared the summary effect sizes and their 95% confidence intervals obtained from these five different approaches. The results obtained from meta-analysis using only extreme exposure categories represent effects of a dosage that is the difference between the lowest and highest exposure dosage, whereas results from meta-analysis with the two-step or one-step approaches represent the effect of a single unit change. To make results of the different methods more comparable, we converted the summary effect sizes from the one-step and two-step methods to reflect the effects of the median of the difference in doses between the extreme intake categories among primary studies within the topic. We made this transformation by multiplying the β coefficient (and its standard error) by the median

difference in doses between the highest and lowest intake categories. All statistical analyses were performed by using STATA SE 11 (Stata Corporation, College Station, Texas). Statistical significance was defined as $p < 0.05$.

3. Results

Twenty-six topics of nutrient-disease associations with published meta-analyses were identified. The number of primary studies within each topic ranged from two to seven. Table 1 describes the characteristics of these topics. Analyzed diseases included various types of cancer, cardiovascular events, cardiovascular mortality, and hip fracture. Analyzed nutrients included omega-3 fatty acids and a variety of micronutrients. In one topic (topic 4), the primary studies reported the nutrient of interest in two different units that were not inter-convertible. Therefore, the primary studies of this topic were stratified by the type of unit used and analyzed separately (topic 4a–b).

3.1. Comparisons between meta-analysis using only extreme exposure categories and meta-analyses using data from all exposure categories

Figure 1(a–c) illustrates the summary effect sizes obtained from three methods with the fixed effect model – meta-analysis using only the extreme exposure categories, meta-analysis with the two-step approach with adjusted data, and meta-analysis with the one-step approach with adjusted data.

Comparing the results between meta-analyses using only extreme exposure categories and meta-analyses using data from all exposure categories, the direction of effect was opposite (i.e., summary OR < 1 in one analysis and > 1 in another analysis) in two topics (topics 8 and 14). In all topics, the confidence interval of the effect size was wider in the meta-analyses using only extreme exposure categories, compared with meta-analyses using all exposure categories. Statistical significance was reached in one analysis but not the other analyses in eight topics (topics 2, 4a, 7, 10, 14, 18, 22, and 26). In five out of these eight topics (topics 2, 10, 14, 22, and 26), results of the meta-analyses for only extreme exposure categories were not statistically significant, whereas results of the meta-analyses using data from all exposure categories were statistically significant. The magnitude of effect was greater (i.e., point estimate further from the null) in the meta-analyses using only extreme exposure categories than in meta-analyses using data from all exposure categories for all topics, except topic 17 where point estimates of the summary effect size of the two analyses were similar.

Figure 2 illustrates the summary effect sizes obtained from random-effects meta-analysis of ORs using only extreme exposure categories, the two-step approach with adjusted data and the one-step approach with adjusted data, for the ten topics that included five or more primary studies. Differences in results between meta-analyses using only extreme exposure categories and meta-analyses using data from all exposure categories in the random-effects model were similar to that in the fixed effect model.

3.2. Comparisons between meta-analyses using the one-step approach and the two-step approach

Figure 1(a–c) illustrates that for all topics, summary effect sizes and their confidence intervals obtained from the two meta-analyses approaches were very similar to two decimal places.

Figure 2 illustrates that the direction of summary effect sizes obtained from random-effects meta-analyses using the one-step and two-step approaches was the same in all topics. Confidence intervals of the effect sizes were generally wider in the meta-analyses with the two-step approach, compared with the one-step approach. In three topics (topics 4b, 13, and 14), statistical significance was reached in meta-analyses with the one-step approach but not the two-step approach. The magnitude of effect was similar between the two approaches in all topics.

3.3. Comparisons between meta-analyses using unadjusted data and meta-analyses using adjusted data

Figure 3(a–b) illustrates the summary effect sizes obtained from fixed effect meta-analyses using unadjusted data, which were derived by using observed counts, and meta-analyses using adjusted data, which were derived by using effective numbers. Results shown were obtained from meta-analyses using the one-step approach.

Comparing the results between meta-analyses using unadjusted data with meta-analyses using adjusted data, the direction of effect was opposite for five topics (topics 8, 14, 15, 24, and 25). In four of these five topics (topics 8, 15, 24, and 25), the odds ratio estimate of the unadjusted analysis was greater than 1, whereas that of the adjusted analysis was less than 1. In all but four topics (topics 4b, 10, 14, and 23), the confidence interval of the effect size was wider in the meta-analysis using adjusted data, compared with the meta-analysis using unadjusted data. Statistical significance was inconsistent in seven topics (topics 1, 3, 6, 8, 14, 21, and 25). In four out of these seven topics (topics 3, 6, 21, and 25), results of the meta-analyses using adjusted data were not significant, whereas results of meta-analyses using unadjusted data were statistically significant. In ten topics (topics 1, 2, 4a, 7, 8, 11, 14, 16, 19, and 22), the magnitude of effect was greater in the meta-analyses using adjusted data, compared with meta-analyses using unadjusted data. These data suggested that there was no consistent pattern of discordance between the two analyses with regards to the direction of effect, statistical significance, or magnitude of effect. The clinical importance of the magnitude of the effects depends on the size of the difference in consumption units relative to what people normally eat and varies by topic.

Figure 4 illustrates the summary effect sizes obtained from random-effects meta-analyses using unadjusted data and meta-analyses using adjusted data for the ten topics that included five or more primary studies. Differences in results between the two analyses in the random-effects model were similar to that in the fixed effect model.

4. Discussion

Meta-analysis of dose-response data in nutritional epidemiology poses four major challenges. First, each study typically contributes several correlated effect sizes. In addition, the mean nutrient intake in each exposure category, which is necessary for dose-response meta-analysis, is typically not reported and has to be imputed or modeled (DuMouchel, 1995; Hartemink *et al.*, 2006; Il'yasova *et al.*, 2005; Shi and Copas, 2004). Third, compared with intervention studies, we have additional sources of clinical and methodological diversity. These stem from non-quantified background exposures, imperfect measurements of exposures, nutrient status, bioavailability of nutrients, bioequivalence of bioactive compounds, multiple and interrelated biological functions, residual confounding and non-linear dose-response relationships, to name some (Chung *et al.*, 2010; Lichtenstein *et al.*, 2009; Russell *et al.*, 2009). Finally, as in all meta-analyses, publication and other selection biases threaten the validity of the results.

We use a systematically assembled database of published meta-analyses on nutrient-outcome associations to empirically compare results with five methods for combining dose-response data. Comparing meta-analysis that uses only data from extreme exposure categories with meta-analysis that uses data from all exposure categories, we found that results sometimes disagreed both in the direction of effect and statistical significance. The magnitude of effect was consistently greater, and the confidence interval was consistently wider in the meta-analysis using only extreme exposure categories. Meta-analysis using only extreme exposure categories ignores data in other exposure categories and introduces heterogeneity because the reference category and the range of exposures within studies can vary widely. In contrast, meta-analyses with either a two-step or a one-step approach use a regression model that incorporates dosage data and provides results that represent the effect of a single dose unit change. In this paper, we were not focused on clinical or nutritional conclusions, but we recognize that for some of the questions we considered, the estimates obtained with different methods might not have dramatically different substantive implications.

The one-step methods greatly simplify fitting of additional (e.g., quadratic and other functions) dose terms when modeling nonlinear dose-response relationships. Further, one-step methods can provide absolute risk predictions and can be used to perform appropriate control-rate meta-regressions. The two-step methods are not suitable for these purposes. Comparing meta-analysis with the two-step approach and the one-step approach, we found that summary odds ratios and their confidence intervals were numerically very similar in the fixed effect model. In the random-effects model, the confidence interval of the effect size was generally wider in the meta-analyses with the two-step approach than with the one-step approach. It was unclear why such differences were not observed in the fixed effect model.

Comparing meta-analysis using unadjusted data and meta-analysis using adjusted data, we found no consistent pattern of discordance with regards to the direction of effect, statistical significance, and the magnitude of effect. In observational studies, statistical adjustment is commonly used to control for the effect of potential confounders. Negative confounding occurs when the confounder causes an underestimation of the effect size, whereas positive

confounding occurs when unadjusted analysis results in an exaggerated effect size (Hennekens and Buring, 1987). Potential negative or positive confounding was observed in some of the topics in the present report. Because the impact of confounder adjustment is rarely predictable, sensitivity analysis comparing results between meta-analysis of adjusted and unadjusted data may provide additional insights into the association under investigation. Of note, the pooling of adjusted effect sizes may be inappropriate when study-specific effect sizes are adjusted for different sets of confounders, representing different type and magnitude of residual confounding. This does not imply a preference for unadjusted results; in such cases, a non-parametric synthesis or even a qualitative synthesis is a practical alternative.

A limitation of this work is that all of the topics in this report included few primary studies (two to seven studies). Seven out of all 26 analyzed topics included only two primary studies. Analyses of reviews using more primary studies are needed to discern more consistent patterns. In addition, the present report examined nutrition topics only. Effect sizes observed in nutrition studies are often small. Differences among the various methods of meta-analyses might have been more apparent for larger effect sizes. We did not find systematic differences among meta-analyses methods by the number of studies in the included topics. Finally, we assumed that the midpoint between the boundaries of ordinal nutrient exposure categories is a good proxy for the mean nutrient intake. However, it is not a comprehensive approach. Il'yasova *et al.* (2005) show an example where different imputations for the mean value can affect the calculation of the dose-response slopes. Hartemink *et al.* (2006) propose fitting parametric distributions to match the exposure categories per study, at which point, the mean exposure per category can be obtained with integration. Cook *et al.* (2001) and DuMouchel (1995) opt to model the exposure levels with interval-truncated distributions. However, it is likely that alternative approaches to calculating the mean exposure in each category of intake would impact all five methods in a similar way. Because we are not interested in clinical or nutritional conclusions, we decided not to perform any additional analyses – as we would do in an applied meta-analysis (see for example Trikalinos *et al.*, 2012).

In summary, meta-analysis of odds ratios that incorporate data from extreme exposure categories only and meta-analysis that uses data from all exposure categories produced different results. This is not surprising, because the former approaches ignore a large percentage of data. We do not recommend performing meta-analysis using only extreme exposure categories, due to its lack of consideration for the actual exposures and exclusion of non-extreme categories. Although conclusions drawn from meta-analyses conducted with the two-step and one-step approach did not differ substantially, the one-step approach frequently had smaller standard errors. Therefore, we recommend using the one-step approach when conducting a meta-analysis with dose-response data. However, this comparison awaits further confirmation with empirical evaluation using larger datasets. Due to the difficulty in assessing confounders in most epidemiological studies, we recommend sensitivity analysis comparing results between meta-analysis of adjusted and unadjusted data to inform the presence and potential magnitude of confounding in the association of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Comparison among fixed effect meta-analyses using three methods: extreme categories only, two-step, and one-step; (b) Comparison among fixed effect meta-analyses using three methods: extreme categories only, two-step, and one-step; (c) Comparison among fixed effect meta-analyses using three methods: extreme categories only two-step, and one-step.

Figure 2.
Comparison among random-effects meta-analyses using three methods: extreme categories only, two-step, and one-step.

Figure 3.
 (a) Comparison between fixed effect meta-analyses using unadjusted and adjusted data; (b)
 Comparison between fixed effect meta-analyses using unadjusted and adjusted data.

Figure 4.
Comparison between fixed effect meta-analyses using unadjusted and adjusted data.

Table 1

Characteristics of included published meta-analyses

Topic	Published meta-analysis	Nutrient analyzed	Outcome analyzed	Number of included primary studies (included sets of data, if applicable)	Analytic method used in the original publication
1	Agnoli <i>et al.</i> , 2006	Beta-carotene	Cervical cancer	2 case-control	Meta-analysis not performed
2	Agnoli <i>et al.</i> , 2006	Folate	Cervical cancer	6 case-control (7 sets)	Extreme exposure categories only
3	Bischoff-Ferrari <i>et al.</i> , 2007	Calcium	Hip fracture	5 cohort (8 sets)	Pooled RR per incremental change in exposure
4a	Ertninan <i>et al.</i> , 2005	Selenium (in ppm)	Prostate cancer	3 case-control, 2 nested case-control	2 step approach, pooling OR with arbitrarily combined exposure categories
4b	Ertninan <i>et al.</i> , 2005	Selenium (in ug/ml)	Prostate cancer	2 case-control (3 sets), 2 nested case-control	2 step approach, pooling OR with arbitrarily combined exposure categories
5	Flores-Mateo <i>et al.</i> , 2006	Selenium	Cardiovascular event	2 case-control, 2 nested case-control	Extreme exposure categories only
6	Gallicchio <i>et al.</i> , 2008	Beta-carotene	Lung cancer	4 cohort	Extreme exposure categories only
7	Gandini <i>et al.</i> , 2000	Vitamin C	Breast cancer	2 case-control, 4 cohort	2 step approach, pooling OR of incremental change in exposure
8	Pittas <i>et al.</i> , 2010	Vitamin D	Hypertension	2 nested case-control	Meta-analysis not performed
9	Zhuo <i>et al.</i> , 2004	Selenium	Lung cancer	2 case-control, 1 nested case-control, 1 cohort	Meta-analysis of mean difference of exposure level between cases and controls
10	Bjelakovic <i>et al.</i> , 2004	Beta-carotene	Gastric cancer	2 case-control	Meta-analysis not performed
11	Chung <i>et al.</i> , 2009a, 2009b	Vitamin D	Breast cancer	2 nested case-control	Meta-analysis not performed
12	Chung <i>et al.</i> , 2009a, 2009b	Vitamin D	Colorectal cancer	5 nested case-control (6 sets)	Meta-analysis not performed
13	Chung <i>et al.</i> , 2009a, 2009b	Vitamin D	Rectal cancer	4 nested case-control (5 sets)	Meta-analysis not performed
14	Chung <i>et al.</i> , 2009a, 2009b	Vitamin D	Colon cancer	4 nested case-control (5 sets)	Meta-analysis not performed
15	Chung <i>et al.</i> , 2009a, 2009b	Vitamin D	Prostate cancer	5 nested case-control	Meta-analysis not performed
16	Hooper <i>et al.</i> , 2004	Omega-3 fatty acids	Stroke	4 cohort	Extreme exposure categories only
17	Hooper <i>et al.</i> , 2004	Omega-3 fatty acids	Cardiovascular event	4 cohort	Extreme exposure categories only
18	Mente <i>et al.</i> , 2009	Beta-carotene	Cardiovascular event	2 cohort	Extreme exposure categories only
19	Mente <i>et al.</i> , 2009	Vitamin E	Cardiovascular event	2 cohort	Extreme exposure categories only
20	Mente <i>et al.</i> , 2009	Vitamin E	Cardiovascular mortality	2 cohort	Extreme exposure categories only
21	Mente <i>et al.</i> , 2009	Vitamin C	Cardiovascular event	3 cohort	Extreme exposure categories only
22	Mente <i>et al.</i> , 2009	Vitamin C	Cardiovascular mortality	4 cohort	Extreme exposure categories only
23	Mente <i>et al.</i> , 2009	Folate	Cardiovascular event	3 cohort	Extreme exposure categories only
24	Wang <i>et al.</i> , 2004	Omega-3 fatty acids	Cardiovascular event	4 cohort	Meta-analysis not performed
25	Wang <i>et al.</i> , 2004	Omega-3 fatty acids	Cardiovascular mortality	7 cohort (8 sets)	Meta-analysis not performed

Topic	Published meta-analysis	Nutrient analyzed	Outcome analyzed	Number of included primary studies (included sets of data, if applicable)	Analytic method used in the original publication
26	Gandini <i>et al.</i> , 2000	Beta-carotene	Breast cancer	2 case-control, 2 cohort	2 step approach, pooling OR of incremental change in exposure

RR, relative risk.
OR, odds ratio.