Methods Research Report

Identifying Signals for Updating Systematic Reviews: A Comparison of Two Methods

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Identifying Signals for Updating Systematic Reviews: A Comparison of Two Methods

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers; as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Identifying Signals for Updating Systematic Reviews: A Comparison of Two Methods

Structured Abstract

Background. Methods of assessing the need for systematic reviews to be updated have been published, but agreement among them is unclear.

Objectives. To compare two methods for assessing the need to update an evidence review, using three evidence reports on the effects of omega-3 fatty acids on cancer, cognition and aging, and cardiovascular diseases (with separate analyses for fish oil and alpha-linolenic acid). The RAND method combines a targeted literature search with the assessments of content experts. The Ottawa method relies on a quantitative and qualitative assessment of the study results from a similar targeted search.

Data Sources. A MEDLINE search was conducted on a limited set of journals, including five pivotal general medical journals and a small number of specialty journals, from 1 year prior to release of the original reports using their search strategies.

Methods. The search results were screened using the original eligibility criteria. Study-level data and findings of existing systematic reviews, randomized controlled trials, and large observational studies addressing the original key questions were abstracted. Using the RAND method, we contacted experts—including members of the original technical expert panels and the original peer reviewers—and sought their opinions regarding the status of the original reports and any new references. The results of the literature reviews and expert opinions were combined to determine the need for updating based on predetermined criteria. Using a modification of the Ottawa method, new trial data were meta-analyzed with the original meta-analysis results. A quantitative signal for the need to update was based on statistical differences with the original meta-analyses. Qualitative signals, such as differences in characterizations of effectiveness, new information about harm, and caveats about the previously reported findings, were sought for outcomes without existing meta-analyses. Agreement between the RAND and Ottawa methods was assessed for each report with the kappa statistic.

Results. Overall agreement between the two methods ranged from “nonexistent” (kappa = 0.19, for fish oil and cardiovascular disease) to “almost perfect” (kappa = 1.0 for cognitive function). Many of the disagreements between the methods were due to a situation where the original review had a Key Question with no evidence and some evidence was identified in the update. In these situations, the RAND method produced a positive signal for updating and Ottawa’s method produced a negative signal. A sensitivity analysis that reclassified these situations as agreement between the two methods yielded much better estimates of agreement: for three of the four conditions, agreement was “substantial” to “almost perfect” and overall agreement was “substantial.”

Conclusions. The RAND method and the modified Ottawa method agree reasonably well in their assessment of the need to update reviews. Both methods alone or in combination may be considered as appropriate tools. Future research would confirm these conclusions for a larger cohort of reviews and assess the predictive validity of the methods with actual updates.

Contents

Executive Summary ES-1
Introduction 1
The Rand Method 1
The Ottawa Method 2
Recent Efforts to Assess the Need for Updating Reviews 3
Methods 5
Literature Search and Data Abstraction 5
RAND Method 5
Soliciting Expert Opinion 5
Compilation of Findings of RAND Method 6
The Ottawa Method 7
Searching for a Quantitative Signal 7
Searching for a Qualitative Signal 7
Searching for an "Other" Signal 8
Compilation of all Findings 8
Results 9
Effects of Omega-3 Fatty Acids on Cognitive Function 9
Overall Results for Cognitive Function 9
Effects of Omega-3 Fatty Acids on Cancer 10
The RAND Method 10
The Ottawa Method-Quantitative Signals for Cancer 11
Overall Results for Cancer 11
Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors 12
Ottawa Method 13
Quantitative Signals 13
Qualitative Signals 13
RAND Method 14
Summary of Discordant Results 15
Comparison of Results Using the RAND and Ottawa Methods 16
Conclusions 18
References 20

Tables

Table A. Overall Comparison and Kappa Statistic for Cognitive Function ES-3
Table B. Overall Comparison and Kappa Statistic for Cancer ES-3
Table C. Overall Comparison and Kappa Statistic for Cardiovascular Disease Markers: Fish oil ES-3
Table D. Overall Comparison and Kappa Statistic for Cardiovascular Disease Markers: ALA ES-3
Table E. Overall Comparison and Kappa Statistic for all Evidence Reviews ES-3
Table 1. University of Ottawa Signals and RAND Indications for the Need for an Update 3
Table 2. Comparison of Signals for Updating the Review on Cognitive Function 9
Table 3. Comparisons of Signals for Updating the Review on Cancer 11

Table 4. Comparison of Signals for Updating the Report on Fish Oil and Cardiovascular Risk Factors 16
Table 5. Comparison of Signals for Updating the Report on ALA and Cardiovascular Risk Factors 16
Table 6. Overall Comparison and Kappa Statistic for Cognitive Function 17
Table 7. Overall Comparison and Kappa Statistic for Cancer 17
Table 8. Overall Comparison and Kappa Statistic for Cardiovascular Disease Markers: Fish oil 17
Table 9. Overall Comparison and Kappa Statistic for Cardiovascular Disease Markers: ALA 17
Table 10. Overall Comparison and Kappa Statistic for all Reviews 17

Appendixes

Appendix A. Search Strategies and Literature Flow
Appendix B. Summary Tables
Appendix C. Evidence Tables
Appendix D. Informational Letters

Executive Summary

The question of how to determine when a systematic review of the evidence needs to be updated is of considerable interest. The rapidity with which new research findings accumulate makes it imperative that the evidence be assessed periodically to determine the need for a full-scale update.

Since 2001, several methods have been devised to assess the need for a systematic review to be updated. Two of these methods were developed by Evidence-based Practice Centers (EPCs).

The Southern California (RAND) EPC at the RAND Corporation developed a method that combines expert opinion with an abbreviated search of the literature published since the original review (the RAND method). An abbreviated search of key journals is conducted using the same search strategy used for the original review. The findings of relevant articles (new systematic reviews, controlled trials, and, if needed, large observational studies) are abstracted; a qualitative assessment is made of whether the new evidence corroborates or diverges from the conclusions of the original review. Simultaneously, the original expert panel members, peer reviewers, and, if necessary, other subject matter experts are polled for their assessments of whether the original conclusions remain valid. Combining the findings of both of these processes, the research team assesses the need to update each of the original conclusions based on a four-point scale: Out of date and definitely in need of updating; Probably out of date and in need of updating; Possibly out of date and in need of updating; Still valid.

The University of Ottawa EPC (UO EPC) developed a method that uses survival analysis and generates a combination of quantitative and qualitative signals for the need to update reviews (the Ottawa method). The method does not involve expert judgment, but instead relies on capturing a combination of quantitative and qualitative signals. Qualitative signals include major changes in the evidence, either a potentially invalidating change in the evidence or simply a major change in the evidence from new meta-analyses or new pivotal trials (defined as trials with a sample size at least three times that of the largest previous trial or that were published in one of the five predetermined most influential medical journals). Explicit criteria are applied to the language used to describe the original findings and that of descriptions of new findings to assess whether the latter constitute significant departures from the former. To establish the existence of a quantitative signal that a review is out of date, an updated meta-analysis is performed combining the results of new trials with the pooled results from the original review using a fixed effects model. Only the results for primary outcomes are analyzed. The new pooled result must meet one of two criteria: a change in statistical significance (from nonsignificant to significant) or a change in effect size of at least 50 percent.

The Agency for Healthcare Research and Quality and the National Institutes of Health Office of Dietary Supplements commissioned the RAND EPC, the Tufts EPC, and the UO EPC to conduct a study to compare the RAND method with the Ottawa method for identifying signals for the need for updating, using three systematic reviews these EPCs had prepared on the effects of omega-3 fatty acids on preventing and treating cancer (RAND), on preventing and treating neurological disorders (RAND), and on risk factors and intermediate markers for cardiovascular disease (Tufts). The cardiovascular disease risk systematic review was divided into two subtopics because the original data were analyzed separately for fish oil and alpha-linolenic acid (ALA). However, we conducted a single literature search and used a single panel of experts for both parts of the cardiovascular review (described below).

Methods

PubMed searches were conducted by UO EPC research librarians using the same search strategies they used for the original reviews but limiting the journals accessed for the cancer and cardiovascular risk factor searches to five key general medical journals and five of the top specialty journals, beginning 1 year prior to the publication dates of the original reviews. Members of the research teams screened titles and abstracts to identify relevant articles, reviewed full text articles, and then hand abstracted the study characteristics and findings into evidence tables.

For the RAND method, we contacted the original members of the Technical Expert Panels (TEP), peer reviewers, and additional experts recommended by the TEP if needed and asked them to assess whether, in their expert opinion, the conclusions in the original review were out of date or still relevant. If an expert asserted that a particular conclusion was out of date, we asked that s/he provide a recent reference. We combined these assessments with the summaries of the newly identified literature and based on the total picture, ranked each conclusion as to whether it was definitely out of date (and in need of updating), probably out of date, possibly out of date, or still valid.

Using the Ottawa method, for Key Questions for which pooled analyses were conducted in the original reviews, we first sought new meta-analyses addressing the same Key Questions. In the absence of those, we identified new randomized controlled trials (RCTs), preferably published in pivotal journals or enrolling populations as large as or larger than those in the largest trials in the original reviews. Pivotal journals were defined as one of the five top general medical journals (New England Journal of Medicine, Lancet, Journal of the American Medical Association, Annals of Internal Medicine, and the British Medical Journal) based on a ranking by journal impact factor. For each new original study, beginning with the largest, we conducted a fixed-effects analysis, pooling the effect size reported in the original meta-analysis and the new result, and looked for a change in effect size or in statistical significance. The need to update conclusions for Key Questions for which no prior pooled analyses had been conducted was evaluated by examining the body of literature for each Key Question or subquestion to assess whether it satisfied the criteria for any of a series of qualitative "signals" of the need for updating, such as a finding opposite to the earlier finding or a finding of substantial harm.

We then compared the assessments produced by the RAND and Ottawa methods. We combined all the RAND signals indicating definitely, probably, and possibly out of date into one category, and compared the conclusions between the methods within each clinical topic area by calculating a kappa statistic. Finally, the Ottawa method did not consider whether to evaluate particular Key Question, where the original evidence review identified no studies but the update search identified at least one relevant study, as "no signal" or as a "signal to update." We performed a sensitivity analysis on these Key Questions.

Results

For the four topics (cancer; neurologic disorders; cardiovascular risk factors, fish oil; and cardiovascular disease, ALA), the range of agreement varied from a kappa of 0.19 (for fish oil and cardiovascular disease markers) to "almost perfect" agreement, with a kappa of 1.0 (for cognitive function). Overall across all 77 conclusions, agreement was classified as "fair." In our sensitivity analysis, where we modified the Ottawa criteria using the sensible rule that a signal to update was triggered when there were any new data on a Key Question for which there were no

data in the original report, agreement was much better: for three of the four conditions agreement between methods was "substantial" or better, and the overall agreement between methods was "substantial" (Tables A–E).

Table A. Overall comparison and kappa statistic for cognitive function

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	3	0	3
RAND Negative	0	2	2
Total	**3**	**2**	**5**

Kappa = 1.0

Table B. Overall comparison and kappa statistic for cancer

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	1 (2*)	3 (2*)	4
RAND Negative	0	18	18
Total	**1(2*)**	**21 (20*)**	**22**

Kappa = 0.36 (0.62*)
*Sensitivity analysis (see text)

Table C. Overall comparison and kappa statistic for cardiovascular disease markers: fish oil

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	4	6	10
RAND Negative	2	14	16
Total	**6**	**20**	**26**

Kappa = 0.30

Table D. Overall comparison and kappa statistic for cardiovascular disease markers: ALA

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	2 (9*)	9 (2*)	11
RAND Negative	0	13	13
Total	**2 (9*)**	**22 (15*)**	**24**

Kappa = 0.19 (+0.83*)
*Sensitivity analysis (see text)

Table E. Overall comparison and kappa statistic for all evidence reviews

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	10 (18*)	18 (10*)	28
RAND Negative	2	47	49
Total	**12**	**65**	**77**

Kappa = 0.36 (0.64*)
*Sensitivity analysis (see text)

Conclusions

In our primary analysis, overall agreement between methods ranged from nonexistent to "almost perfect." However, we judge our sensitivity analysis, which makes a reasonable modification to the Ottawa method, as being a more useful measure of agreement between the two methods. In our sensitivity analysis, agreement was "substantial" or better in three of the four conditions. Overall agreement between methods was "substantial." Many of the situations where the methods resulted in disparate recommendations were of the same general form, namely situations where "other" signals were triggered with the Ottawa method (but these signals were not considered as indicating that the review was out of date) whereas in RAND's method, the judgment was that the new evidence was sufficient to conclude that the original review was probably out of date. For example, for the finding related to the risk of developing

one particular type of cancer, there were two existing cohorts with many thousands of subjects, neither reporting any association of fish or omega-3 fatty acids with incidence. To this evidence was added a new case control study (with 600 cases, but not meeting the pivotal article criteria) that reported an association. So, to increase the agreement between the two methods, either these kinds of "other" signals could be elevated to the level of a qualitative signal, or we would need to learn, using the RAND method, not to judge this kind of new data as being sufficient to consider the original conclusion as possibly out of date.

Our results support the hypothesis that either method can be used with confidence that it produces results that are about the same as the other method. However, stronger conclusions will await future replications of our study using different systematic reviews. A decision to update a systematic review might also be informed by the application of both methods, with the results compared to provide additional validation or to highlight areas of disagreement. Factors that may influence the choice of method, although not tested explicitly in this project, could be any of the following:

- Level of expert engagement in the research topic (low levels favor Ottawa)
- Quality and variation in study designs found in the new evidence (low levels favor RAND, as Ottawa is designed with high-quality trials in mind)
- Desire for considering absolute levels of prior evidence, rather than only relative levels (high desire favors RAND, which allows more subjective application of updating signals; Ottawa's relative change signals do not take into the account whether there were originally 2 or 50 studies)
- Desire for a transparent, consistent signaling method that maximizes interrater reliability (high desire probably favors Ottawa, since signals have less flexibility).

In the process of conducting the two update signal methods in parallel, we ignored the findings of one method in evaluating the conclusions of the other. In particular, in conducting the qualitative and quantitative Ottawa methods, we did not include the new studies supplied to us by the domain experts. This artificial approach highlighted that there is not an either/or decision to be made as to which update signal method should be applied in the future. It seems logical that a hybrid approach may be most reasonable, using both input from subject matter experts and searching for pivotal trials or meta-analytic evidence of quantitative signals. Additionally, consideration should be given to the utility of other kinds of signals, such as the continuing use and importance of the original systematic review, the continuing use of the interventions assessed in the review, and whether there is an opportunity for updating the review to lead to a change in practice.

Additionally, although it would have been desirable to compare the resources involved in applying each method, we found it impossible to do that because each EPC was conducting the comparison of the RAND method and the Ottawa method for the same evidence reviews, and the same EPC staff were participating in both applications. Qualitatively, we note that the Ottawa approach alone would involve less work than the RAND method if one of the larger RCTs that were assessed triggered a quantitative signal, as occurred with multiple outcomes for fish oil in the cardiovascular report and the addition of a very large (N=18, 645) RCT from Japan.

Conversely, when no quantitative signal is found even after adding all seven new RCTs, as seen in the assessment for the cancer review, the Ottawa method may take more work than the RAND method.

Further consideration should be given regarding what to conclude when a single expert votes that a topic is out of date and how to interpret experts' votes that a topic is outdated if no

supporting evidence is provided. The cardiovascular review, in particular, had several instances where this was the case. For example, one of six experts stated that the original review's finding on blood pressure was out of date (fish oil supplementation results in small decreases in systolic and diastolic blood pressure). However, the one new article reporting on blood pressure was a systematic review that had very similar conclusions to the EPC review. Similarly, the new evidence on fasting glucose and fasting insulin provided by the experts (two of whom stated that the review's conclusions were outdated) were consistent with the original review. And one expert said that the conclusions on coronary restenosis are outdated, but provided no supporting evidence. Notably, sticking to the protocol, the Tufts EPC did not press the experts to provide supporting new evidence beyond the original request in the questionnaire. In the future, followup with the experts could be done easily. Analogously, further consideration needs to be given to the situation where a single trial provides a quantitative signal, where experts did not judge this new evidence to be a signal for updating, and the original EPC also judged the new evidence to be inconclusive in changing the original finding. This situation occurred in the fish oil and low-density lipoprotein–high-density lipoprotein outcomes with the addition of the above-mentioned Japanese trial.

We also had some difficulties implementing the RAND method when evaluating outcomes with sparse data. This difficulty was particularly evident for several cardiovascular risk factor outcomes of ALA intake. Specifically, we had difficulty determining whether outcomes with zero to two studies in the original review were outdated when there were one or two new studies with small or non-significant results. We found that we came to different conclusions each time we reviewed the new evidence.

Finally, we cannot compare the predictive validity of the RAND and Ottawa methods as no actual updates of the original reviews have been done. Such a predictive validity analysis will need to wait until reports assessed for signals are actually updated. When several updates have been performed on evidence reviews that have been analyzed for signals, it will be useful to analyze whether the Ottawa and RAND methods, or a combination of the two, accurately predict whether the updated systematic review will come to new conclusions compared to the original reviews. Additionally, two modifications to the Ottawa method are proposed for immediate use:

(1) The extension of the qualitative signals criteria to include nontrial data for those Key Questions where the original review included nontrial evidence.

(2) The designation of new evidence—in a situation where the original review had no evidence—as a signal for updating.

Introduction

The question of how to determine when a systematic review of the evidence needs to be updated is of considerable interest. Changes in the evidence can have significant implications for clinical practice guidelines and for clinical and consumer decisionmaking that depend on valid systematic reviews as their foundation. The rapidity with which new research findings accumulate makes it imperative that the evidence be assessed periodically to determine the need for a full-scale update of systematic reviews.

The science of identifying signals for updating systematic reviews has been developing for the past decade. Prior to 2001, no methods or criteria existed to determine whether evidence-based products remained valid or whether the evidence underlying them had been superseded by newer work.

The Cochrane Collaboration has striven to update its systematic reviews biennially (driven by policy). However, such updates involve a huge investment of time and effort and might not be appropriate for all topics. Thus, in 2005, members of the Collaboration assessed whether 4-year updates might be adequate for some topics by comparing the results and conclusions of 1998 reviews with their 2002 updates. Among 254 updated reviews, only 23 (9 percent) had a change in conclusion, supporting the idea that a priority approach, rather than an automatic time-based approach, should be used to determine the need for an update.[1]

Since 2001, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) program has been conducting studies to develop methods to assess the need for updating evidence reviews, as detailed below.

The RAND Method

In the late 1990s, AHRQ commissioned the Southern California (RAND) Evidence-based Practice Center at the RAND Corporation to determine whether their clinical practice guidelines needed to be updated and how quickly guidelines go out of date. RAND first devised a conceptual model that consisted of six situations that would require a guideline to be updated or withdrawn.[2] These situations included changes in (1) the available interventions, (2) the evidence on the benefits and harms of existing interventions, (3) the outcomes that are considered important, (4) the evidence that current practice is optimal, (5) the values placed on outcomes, and (6) the resources available for health care. Their assessment of the need to update the AHRQ guidelines did not take the final two situations into account as the measurement of these situations was considered beyond the scope of the process. The scope of the task also required that, rather than conducting a series of new systematic reviews, RAND would devise a method that could be feasibly applied to a large number of guidelines. Reasoning that any new findings that differed from the previous findings with sufficient magnitude to warrant reconsideration of a guideline would be both published in a major journal and familiar to experts in the field, they used a combination of a literature search focused on predefined major journals and the guidance of experts from relevant disciplines as a more pragmatic way to help identify potentially significant new evidence. Using this approach, they determined that out of 17 guidelines, new evidence and expert judgment indicated that 7 required a major update; 6 required a minor update; 3 were judged as still valid; and no conclusion could be reached for one guideline. Survival analysis indicated that about half the guidelines were outdated in 5.8 years; at 3.6 years, more than 10 percent of the guidelines were outdated.[3]

In 2008, RAND was given the task to adapt its abbreviated method to assess the need for updating the comparative effectiveness reviews that had been prepared to that point. Briefly, the application of the method included the following steps. For each review, RAND conducted an abbreviated search of key journals using the same search strategy used for the original reviews, abstracted the findings of relevant articles (new systematic reviews, controlled trials, and if needed, large observational studies), and made a qualitative assessment of whether the new evidence corroborated or diverged from the conclusions of the original reviews. RAND also polled the original technical expert panel members, peer reviewers, and if necessary, other subject matter experts for each review for their assessments of whether the original conclusions remained valid. Combining the findings of both of these processes, RAND assessed the need to update each of the original conclusions based on a four-point scale: Out of date and definitely in need of updating; Probably out of date and in need of updating, Possibly out of date and in need of updating; Still valid (Table 1). The methods and the results of this assessment were written up in a final evidence report that was posted on the EPC Web site and are described in further detail in the Methods chapter of this report.[4]

The Ottawa Method

Shojania and colleagues at the University of Ottawa devised a method using survival analysis to assess the need to update reviews and tested it among 100 meta-analyses published from 1995 to 2005.[5] The method did not involve expert judgment, but instead relied on capturing a combination of quantitative and qualitative signals.

Qualitative signals included major changes in the evidence, either a potentially invalidating change in the evidence or simply a major change in the evidence from new meta-analyses or new pivotal trials (defined as trials that had a sample size at least three times that of the largest previous trial or that were published in one of the five predetermined most influential medical journals). Explicit criteria were applied to the language used to describe the original findings and that of descriptions of new findings. Specifically, the following qualitative signals were used to assess a new body of literature or large or pivotal new studies (Table 1).

To establish the existence of a quantitative signal that a review was out of date, they performed updated meta-analyses combining the results of new trials with the pooled results from the original review using a fixed effects model. Note that the Ottawa method does not require recreating the original pooled analysis. Rather, the original pooled results are considered as one point entering into a new fixed effects model. Only the results for primary outcomes were analyzed. The new pooled result had to meet criteria B1 or B2 in Table 1.

Because of the less-than-ideal quality of the published literature (e.g., the paucity of large randomized controlled trials [RCTs]), the researchers also established a category of "Other" signals. The criteria included a major increase in the number of new studies or a new study with at least three times the number of participants as previous studies.[6]

Among the 100 reviews (which ranged in time since publication approximately 1 to 10 years), 57 percent showed some sign of being out of date. The median length of survival without displaying such a signal was 5.5 years; although 7 percent of the reviews were out of date by the time they were published, only 4 percent were out of date within a year of the end of the search period. Thus, like the RAND study, this study showed the need for frequent, and in some cases almost immediate, updating. The apparent need for more frequent updating was related to topic and to the study heterogeneity found in the original evidence review.

Table 1. Ottawa signals and RAND indications for the need for an update

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decisionmaking.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

To compare the comprehensiveness and effort required to employ the RAND abbreviated method with that of a typical full-blown literature search, Gartlehner and colleagues created a streamlined version of the RAND method.[7] They then implemented both the abbreviated and the "traditional" approaches to assess the need to update the 1996 U.S. Preventive Services Task Force Guide to Clinical Preventive Services. The study found that although the abbreviated RAND method identified fewer eligible studies than the "traditional approach," Task Force members who were acting as project liaisons rated none of the studies missed by the abbreviated method as important to assessing the need for an update to the guidelines. Thus, they deemed the revised approach to be an efficient and acceptable method for assessing the need to update a guideline.[8]

Recent Efforts to Assess the Need for Updating Reviews

In 2010, AHRQ and the National Institutes of Health Office of Dietary Supplements (ODS) commissioned the RAND EPC, the Tufts EPC at Tufts Medical Center, and the University of Ottawa (UO) EPC to conduct a study to compare the RAND and Ottawa methods for identifying signals for the need for updating. The methods were compared using three evidence reviews conducted by these EPCs on the effect of omega-3 fatty acids for preventing and treating cancer,[9] preventing and treating cognitive disorders,[10] and on risk factors and intermediate markers for cardiovascular disease[11] as test cases. This review presents the results of that comparison. To our knowledge, there has been no prior comparison of these two methods. Indeed, we know of no prior comparison of any methods to detect signals for updating. Furthermore, we are unaware of any major organization currently implementing a systematic assessment of reviews for signals for updating, although interest in this topic is high.

The three original evidence reviews were chosen because they were of interest to ODS, one of the sponsors of the project, who want information about the possible need to update these reviews while also contributing to the science of determining signals for updating. The original

evidence reviews were published in 2004 and 2005. The collaboration that produced the reviews, together with a summary of the review topics, was described in a previous publication.[12] Briefly, the cancer review examined incident cancer and gastrointestinal cancer recurrence after surgery; 25 studies reported data on 22 clinical and intermediate cancer outcomes.[9] Three meta-analyses were performed. The neurological disorders review examined dementia or cognitive function decline in the elderly or those with Parkinson's disease, and multiple sclerosis; 12 studies reported data on 5 clinical and intermediate outcomes.[10] No meta-analyses were performed. The cardiovascular evidence review examined the effect of omega-3 fatty acids on 24 cardiovascular risk factors and intermediate outcomes.[11] Following the structure of that review, for the current analysis, we treat the evaluation of fish oils and alpha-linolenic acid as two separate evidence reviews.

Methods

Literature Search and Data Abstraction

The literature searches were conducted by the University of Ottawa Evidence-based Practice Center (UO EPC) using the same key terms as used for the original reviews (see Appendix A). The searches were conducted using a modification of the RAND and Ottawa methods. This method employed an abbreviated literature search strategy that focused on five major (pivotal) general-interest medical journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, The Lancet, and New England Journal of Medicine; as per the Ottawa method) supplemented with a small number of specialty journals tailored to each topic, as recommended by content experts at RAND.[3] In addition, we included journals that had published three or more articles cited in the original reviews (see Appendix A). However, for the review on cognitive function, the combination of generalist and specialty journals (based on the original review) resulted in a very small number of new titles; therefore, the decision was made to augment that search with an additional search conducted without restricting journals. Furthermore, since the previous evidence base for cognitive function was very small and included many population-based studies with short-term followup periods, an additional search was done to identify whether the previous studies had been updated with longer-term followup data. The starting dates for all searches were set at 1 year prior to the ending dates of the original searches to capture any studies not included in the original searches. The literature search results were sent to the relevant EPC for further analyses (cognitive function and cancer to the RAND EPC; cardiovascular risk factors to Tufts EPC).

The title/abstract lists from the literature searches were screened by members of the respective EPC staffs (dually for cancer and cognitive function, singly for cardiovascular risk factors, based on available resources and numbers of abstracts to be screened and articles to be extracted) and the selections were combined. Full-text articles were obtained for all titles that appeared relevant, and the articles were further screened for inclusion. Eligibility criteria were limited. The only factors considered were whether the study being reported was relevant to one of the Key Questions from the original EPC reviews and whether the study design met the same criteria as for the original reviews. In addition, relevant systematic reviews were also included. For the RAND method, we added any articles cited or recommended by the experts (see below) not already identified in the literature searches. Single reviewer abstraction was done for study design, interventions, pertinent study participant characteristics, outcomes, and findings to a separate evidence table for each of the original reviews.

RAND Method

Soliciting Expert Opinion

Based on the method used in the RAND report on updating comparative effectiveness reviews, for each of the reviews we collected a list of topic experts from the original reviews, Technical Expert Panel (TEP), peer reviewers of the reports, and other subject matter experts. For the report on cognitive function, several of the original TEP members and reviewers responded that they were no longer actively pursuing research in the field, and some provided us with names of other experts: thus, we contacted those experts as well as several experts suggested by other TEP members and reviewers. Each expert who agreed to participate

completed a disclosure of interest form. We aimed to include at least four experts for each review. Appendix B shows the number of experts contacted for each review. For each original review, we created a form that included the original Key Questions and conclusions. The Key Questions were taken verbatim from the original reviews. The review's conclusions were based on information in the Executive Summary, Discussion chapter, or other summaries. To the extent possible, we quoted the conclusions from the original reviews. For each set of conclusions, we asked the experts whether all of the findings were "almost certainly still supported by the evidence" and, if the answer was "no," to provide us with any new evidence known to them. For the cardiovascular risk factor review we also asked the experts whether selected risk factors should not be included in any future update and to list additional cardiovascular risk factors or intermediate markers of cardiovascular disease that should be included in a future review on omega-3 fatty acids (Appendix D). We further instructed the experts that we did not expect them to conduct a literature search before providing an assessment, rather if they answered "yes" to the question "has there been new evidence that may change this conclusion," they were to provide the citations to published studies (see informational letters in Appendix D).

Compilation of Findings of RAND Method

For each review, we constructed a summary table that included the Key Questions, the original conclusions, the findings of the new literature search, and the expert assessments. Based on this information, we arrived at a set of conclusions, which was added to the summary table. Based on the original RAND methodology, we used a four-category scheme to assess the conclusions in terms of the evidence that they might need updating.[4] All conclusions about signals for the possible need to update a review were determined by consensus in several rounds of group discussions within the EPCs based on all relevant information available to us. Subject matter experts did not participate in these discussions. In addition, we reevaluated our conclusions after discussions among the EPCs about our methods. The four categories are:

1. Original conclusion is still valid, and this portion of the original review does not need updating.
2. Original conclusion is possibly out of date, and this portion of the original review may need updating.
3. Original conclusion is probably out of date, and this portion of the original review may need updating.
4. Original conclusion is out of date.

In making the decision to classify a review conclusion into one category or another, we used the following factors when making our judgments:

- If we found no new evidence or only confirmatory evidence and all responding experts judged the conclusion as still valid, we classified the conclusion as still valid.
- If we found some new evidence that might change the conclusion, and/or a minority of responding experts (fewer than half) judged the conclusion as having new evidence that might change the conclusion, we classified the conclusion as possibly out of date.
- If we found substantial new evidence that might change the conclusion, and/or a majority of responding experts (half or more) judged the conclusion as having new evidence that might change the conclusion, then we classified the conclusion as probably out of date.
- If we found new evidence that rendered the conclusion out of date or no longer applicable, we classified the conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited

search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a supplement from the market.

The Ottawa Method

To apply this method, we used the same literature search output as used for the RAND method but not the studies added by the domain experts. As described in the introduction, the method relies on the search for any of three types of "signals" of the need to update: a qualitative signal, a quantitative component, and an "other" signal. The type of signal sought depends on the body of literature: if the response to a Key Question in the original review included a meta-analysis, a quantitative signal can be sought, using an algorithm developed by the UO EPC. If no previous meta-analyses could be conducted, a qualitative or other signal is sought. We used the same within- and between-EPC group consensus approach to determine signals as we did for the RAND method. We determined signals for the RAND and the Ottawa methods during the same discussions about the evidence. We did not have separate, independent meetings for each method.

Searching for a Quantitative Signal

The original Ottawa method confined the search for a quantitative signal to one of the primary outcomes or any new mortality outcome. For this report, we conducted the quantitative search for each of the main Key Questions for which a meta-analysis result was reported in the original review or associated journal articles (we excluded questions that assessed outcomes in laboratory animals or in vitro models). For each new original study, beginning with the largest, we conducted a fixed effects analysis, pooling the effect size reported in the original meta-analysis and the new result. This process was repeated with each subsequently smaller trial until we found a signal as defined by the Ottawa method (a change in statistical significance or a relative change in effect magnitude of at least 50 percent) or until all new studies were included in the analysis.

Searching for a Qualitative Signal

Qualitative signals were ascertained by comparing the findings of the original reviews with the findings of new systematic reviews or "pivotal trials." As defined by the Ottawa method, pivotal trials were published in one of the pivotal journals described above or trials published in nonpivotal journals but with at least three times the number of participants as the previous largest trial. Lacking such trials, all relevant new studies were reviewed.

The comparison took into account the following criteria: findings that invalidate the previous findings, and "major changes in evidence," such as evidence that a treatment is in/effective for a specific patient subpopulation not previously considered. The following Web site provides further information on the method: www.ohri.ca/UpdatingSystRevs (see Table 1 for further details). Qualitative signals were assigned based on the entire body of new studies that addressed a particular outcome.

The Ottawa method is silent on how to assign a signal when the original review had no trials addressing a specific question and there are new small trials. This is because the original Ottawa method started with published systematic reviews, for which by definition, there already exist randomized controlled trials (RCTs) sufficient to do a review. However, Agency for Healthcare Research and Quality evidence reviews are based on Key Questions, and situations arise where a

Key Question has no existing eligible evidence. We took the conservative approach and labeled these situations where there was no evidence in the original review and some evidence in the update search as "no signal" since the Ottawa method did not define this situation a priori. As a sensitivity analysis, we also assigned these situations as A4 (important changes in effectiveness short of "opposing findings"; see Compilation of All Findings section below), reasoning that had the Ottawa method been required to consider this situation, the method would have judged the existence of some new evidence as being a signal for updating.

Searching for an "Other" Signal

"Other" signals were sought for Key Questions for which there were no prior meta-analyses and no RCTs, such as questions for which only large cohort or case-control studies were identified. The criteria included a major increase in the number of new studies or a new study with at least three times the number of participants as previous studies. These criteria had to be adapted to account for situations such as a large number of new but smaller studies, when the studies in the original review had been large prospective cohort studies and the new studies were largely smaller nested case-control studies. The results of applying the Ottawa method were documented in the last column of the summary tables for each review.

Compilation of All Findings

The RAND assessments were compared with the Ottawa assessments for each Key Question and each outcome, and a kappa statistic was calculated for each. As a sensitivity analysis, we also calculated an additional kappa, assigning the "no prior evidence" situation as a signal for updating in the Ottawa method. We used the Landis and Koch[13] interpretation of values of kappa to determine the level of agreement.

κ	Interpretation
< 0	Poor agreement
0.0 – 0.20	Slight agreement
0.21 – 0.40	Fair agreement
0.41 – 0.60	Moderate agreement
0.61 – 0.80	Substantial agreement
0.81 – 1.00	Almost perfect agreement

Results

This chapter presents the results of our comparisons of the RAND and Ottawa update methods for each of the three reviews in turn.

Effects of Omega-3 Fatty Acids on Cognitive Function

The literature search identified 1,009 articles from an unrestricted set of medical journals, and experts suggested an additional 5 articles, for a total of 1,014 articles whose abstracts were reviewed for relevance. Of those, 89 articles were selected for full-text review, and 26 were abstracted. Selection criteria were consistent with those used in the original review. Specific exclusion criteria were: no outcomes of interest, weak study design (i.e., cross-sectional, descriptive, or narrative review), study population <18 years old, cognitive/neurological condition was mental health disease or trauma related, and no specific measure of fat intake attributable to fatty fish/omega-3 fatty acids. Systematic reviews were reference mined but not abstracted. Since nearly all of the original studies listed in systematic reviews were already identified and abstracted from the Ottawa reference search, also abstracting the systematic reviews would have resulted in double counting of many study populations. The article flow is in Appendix A, and detailed article abstractions are in Appendix C.

Informational letters were sent to 25 experts, of whom 5 returned responses. The remaining 20 individuals cited time constraints and lack of knowledge about recent evidence in the field. The poor response rate is attributable to the small number of experts who actively follow this area of research; several of those who responded also indicated they had little knowledge about the current state of research related to omega-3 fatty acids and cognitive or neurological disorders.

Overall Results for Cognitive Function

Both the Ottawa and RAND updating signals had an absolute agreement of 100 percent and kappa of 1.0 for the 5 Key Questions related to the role of omega-3 fatty acids in cognitive and neurological disorders. Key Questions 1–3 were determined to be out of date, and Key Questions 4–5 were considered up to date by both methods. Appendix B includes a detailed summary of the RAND and Ottawa-based conclusions for each Key Question. Our conclusions also did not change when articles recommended by experts were excluded, although experts did recommended two new articles that did not appear in the Ottawa literature search due to their very recent publication.

Table 2. Comparison of signals for updating the review on cognitive function

RAND	Ottawa Positive	Ottawa Negative	Total
Definitely out of date	0	0	3
Probably out of date	3	0	0
Possibly out of date	0	0	0
Still valid	0	2	2
Total	**3**	**2**	**5**

We note that since Ottawa's updating signals were designed around the characteristics of clinical trials, and since much of the evidence for cognitive/neurological disease was from population-based studies, we used modified interpretations to determine whether evidence met an Ottawa qualitative signal for updating. Namely, none of the articles reviewed was from a

major general medical journal—all were from specialty journals, so it was not possible to meet Ottawa's original definition of a pivotal trial in that respect. Also, for Key Question 2, the largest study group included in the new evidence (n=8,085) was less than three times as large as the largest study group in the original review (n=5,386). Unlike clinical trials, where the original study population might be modest (one example in this report is a sample size of 20), in large cohort studies, a threefold change in sample size may be more difficult to achieve and may not mean the same thing as a threefold change in sample size for a clinical trial. Without these modified definitions, Key Questions 1–3 would not have met strict Ottawa criteria for updating. As a group, and with input from the original developers of the Ottawa method, we discussed these modifications and believe that with them the new evidence is consistent with Ottawa's original intent and approach to signaling for updates.

In addition to the five Key Questions evaluated in the original review, two articles describing a new but related Key Question were identified—the effect of omega-3 fatty acids on treatment of Huntington's disease. While this review focused on evaluating whether existing Key Questions were still up to date, the identification of a new study question might be interpreted as a broader signal about whether the entire review is out of date.

Effects of Omega-3 Fatty Acids on Cancer

The literature search identified 125 articles from a combination of the 5 pivotal medical journals and 6 specialty journals suggested based on their rate of citation in the original review: American Journal of Clinical Nutrition, The European Journal of Clinical Nutrition, JPEN Journal of Parenteral & Enteral Nutrition, The American Journal of Public Health, The American Journal of Epidemiology, and BMC (Biomed Central) Cancer Journal. Experts suggested an additional 15 articles. In addition, a small independent search was conducted for articles that cited an article recommended by one of the experts on the topic of omega-3 fatty acids and cancer treatment, because the search design did not capture articles on this topic; this search identified 16 potentially relevant articles. Thus, abstracts for a total of 162 articles were reviewed for relevance. Of those, 67 articles were selected for full-text review, and 47 were abstracted, of which 20 were subsequently rejected. Selection criteria were consistent with those used in the original review. Specific exclusion criteria were: no outcomes of interest, weak study design (i.e., cross-sectional, descriptive, or narrative review), and no specific measure of fat intake attributable to fatty fish, fish oil, or total or specific omega-3 fatty acids. Systematic reviews were reference mined but not abstracted. Nearly all of the original studies listed in systematic reviews were already reviewed in the original review, or were identified and abstracted from the University of Ottawa Evidence-based Practice Center (UO EPC) search. The article flow is in Appendix A, and detailed article abstractions are in Appendix C.

The RAND Method

Informational letters were sent to 13 experts, of whom 7 returned responses. The remaining six individuals did not respond. Of those who responded, at least one cited a lack of knowledge about the current research in the field, and at least two provided responses for only one or two of the Key Questions. However, several recommended articles, including one that responded to Key Question 2 (for which no titles had appeared in the UO EPC literature search, apparently due to search design). A number of the other articles cited were already included, either in the original review or in the results of the search for this report.

The Ottawa Method - Quantitative Signals for Cancer

We followed methods for detecting a quantitative signal as discussed in the original Ottawa method report.[5, 6] For each of the three previously pooled outcomes, the original results from the meta-analysis were pooled using a fixed effects model with data from each of the new studies.

Since there were no pivotal trials, we started with the largest trial. After each study was pooled, the results were reviewed to see if one or more of the quantitative signals were met. The quantitative signals included: (1) a change in statistical significance (must have a p-value <0.04 or >0.06), (2) a relative change in effect size of at least 50 percent, (3) a significant difference between the old and new point estimates. If one of the quantitative signals appeared as true, then no new studies were added for a given outcome. As long as a quantitative signal did appear, then studies were added until a quantitative signal was detected or there were no studies left to add.

The original review provided meta-analytic poolings for three outcomes (complications, mortality, and length of hospital stay). Of the 10 new articles identified for this report [14-23], 7 reported at least one of the previously used outcomes.[15-21] Three studies reported on mortality,[15, 16, 19] four studies reported on length of stay,[15, 18, 20, 21] and all seven reported on complications. For the mortality outcome, the original review showed a nonsignificant odds ratio (95% confidence interval [CI]) of 1.25 (0.64, 2.48). None of the three signals was detected after adding any of the three studies that reported mortality. The original review estimated a relative risk of 0.57 (0.46, 0.72) for the complications outcome. Again, no quantitative signal was detected when adding any of the seven new trials that reported complications. The pooled mean difference (95% CI) in the original review for length of hospital stay was −3.17 (−4.12, −2.23). Adding the four new trials did not allow us to detect a quantitative signal.

Overall Results for Cancer

The Ottawa and RAND updating signals agreed for 19 of 22 Key Questions/subquestions (see Table 3), resulting in a kappa of 0.36 for all of the Key Questions related to the role of omega-3 fatty acids in preventing and treating cancer. In the sensitivity analysis, the kappa statistic was 0.62. For reference, Appendix C includes the evidence tables constructed from the literature identified in the update searches.

Appendix B includes a detailed summary of the RAND and Ottawa-based conclusions for each Key Question.

Table 3. Comparisons of signals for updating the review on cancer

RAND	Ottawa Positive	Ottawa Negative	Total
Definitely out of date	0	1	1
Probably out of date	1	2	3
Possibly out of date	0	0	0
Still valid	0	18	18
Total	**1**	**21**	**22**

In applying the Ottawa signaling criteria to the studies in this report, a number of modifications were needed. First, the original review was able to pool results for only a small proportion of the outcomes, all of which were outcomes of trials assessing the effect of perioperative omega-3 fatty acid-supplementation of patients who underwent surgery to treat upper-gastrointestinal tract cancers (postoperative complications, length of hospital stay, and mortality). Therefore, we were able to seek a quantitative signal only for these outcomes (and found none). Second, the entire body of evidence for cancer prevention was from population-

based studies, both prospective cohort and nested case control studies; therefore, we used modified interpretations of the Ottawa qualitative signals to determine whether the evidence met an Ottawa qualitative signal for updating. As a group, and with input from the original developers of the Ottawa method, we discussed these modifications and believe that with them the new evidence is consistent with Ottawa's original intent and approach to signaling for updates. Only one of the articles reviewed was from a pivotal (i.e., major general medical) journal—the remainder were from specialty journals, and that one article was one of a number of articles that presented conflicting findings, so it was not possible to meet Ottawa's original definition of a pivotal trial for any of the Key Questions.

There were three instances where the RAND method produced a signal suggesting the probable or definite need for updating for a particular question, whereas the Ottawa method did not produce a quantitative or qualitative signal for the need to update. All three were similar: In two cases there was a modest amount of evidence in the original review and in the third case there were no relevant studies in the original review; the update search identified a small number of new studies (1, 1, and 2 new studies) that did not meet Ottawa criteria for a qualitative signal but were judged by the RAND method as a signal that the original conclusion was probably or definitely out of date.

Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors

The literature search identified 613 articles. We screened the abstracts using the same eligibility criteria as for the original review. We included the cardiovascular risk factors and the outcome-specific study design features listed in Table 3.1 (page 35) of the original review.[11] We included only studies with omega-3 interventions (diet or otherwise) less than or equal to 6 g/day. We also included narrative and systematic reviews if they were relevant to this topic.

Based on the sources of studies in the original review, in addition to the five "pivotal" journals, we searched the American Journal of Cardiology; the American Journal of Clinical Nutrition; the American Journal of Medicine; Arteriosclerosis, Thrombosis, and Vascular Biology; Atherosclerosis; the British Journal of Nutrition; Cardiovascular Research; Diabetes Care; Diabetologia; the European Heart Journal; the European Journal of Clinical Nutrition; the Journal of Nutrition; Lipids; Thrombosis and Haemostasis; Thrombosis Research; and Vascular Medicine.

After full-text screening, data from 60 articles (6 of which were systematic reviews) were then extracted. In addition, 31 articles were later identified by expert opinion, 5 of which had already been accounted for. After screening the remaining suggested articles, 12 of these were ultimately included (for evaluation of the RAND method only).

In total, 15 experts were contacted to provide their input for this topic. These included all of the peer reviewers and Technical Expert Panel members of the 2004 review, as well as other topic experts. Of these, six replied with the completed form as well as a completed disclosure of interest form.

Ottawa Method

Quantitative Signals

Based on the original review and accompanying journal articles,[24, 25] there were nine outcomes for which meta-analyses were reported. The meta-analyses evaluated the effect of fish oils on total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides, systolic and diastolic blood pressure (in people without diabetes mellitus), hemoglobin A1c, fasting glucose, and coronary artery restenosis by arteriography. New trial evidence was found for all outcomes except coronary artery restenosis. A very large trial from Japan compared eicosapentaenoic acid supplementation with placebo in 18,645 participants (4,565 of whom had impaired glucose metabolism [Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS)]).[26] This trial found discordant results with almost all other trials (both old and new trials) for several outcomes. Thus, a quantitative signal was found after adding this single trial to the meta-analyses for total cholesterol (from a null effect to a statistically significant net reduction with fish oil), LDL (from a statistically significant net increase with fish oil to a null effect), HDL (from a statistically significant net increase with fish oil to a null effect), systolic and diastolic blood pressures (from statistically significant net decreases with fish oil to a null effect on systolic blood pressure and a statistically significant increase in diastolic blood pressure), and fasting glucose (from a nonsignificant effect to a smaller, but statistically significant, net increase with fish oil). No quantitative signal was found for triglycerides after the addition of 10 new trials. No quantitative signal was found for hemoglobin A1c after the addition of four new trials.

Of note, however, due to incomplete reporting, we had to estimate the standard errors of the net differences from JELIS. Given the very large size of the trial, and thus the very small standard errors, we ended up estimating P values of the net differences that were discordant with the study conclusions. This impacted the meta-analyses. The study reported no significant effect on diastolic blood pressure, however our estimate yielded a very small but statistically significant net increase (1 mm Hg; 95% CI 0.7, 1.3), which resulted in a statistically significant summary estimate. A similar set of discordant results occurred with fasting glucose.

Qualitative Signals

Fish Oil

The numbers of pivotal trials identified for total, LDL, and HDL cholesterols, and blood pressure were 5, 4, 6, and 7, respectively. Among these pivotal trials, one very large trial (JELIS, N = 18,645) reported findings that disagreed with the results from the original review for total, LDL, and HDL cholesterols, and systolic and diastolic blood pressure in people with diabetes, and therefore triggered qualitative signals for these outcomes.

Pivotal trials were identified for triglycerides (three studies), lipoprotein (a) (five studies), apolipoprotein A-1 (one study), apolipoprotein B (two studies), blood pressure in people without diabetes (six studies), hemoglobin A1c (four studies), fasting glucose (five studies), fasting insulin (nine studies), C-reactive protein (CRP) (five studies), fibrinogen (three studies), factor VII (three studies), non-Willebrand factor (three studies), platelet aggregation (one study), carotid intima media thickness (one study), but the findings of these trials did not oppose the results of the original review. No pivotal trials were identified for apolipoprotein B-100, LDL

apolipoprotein B, factor VIII, coronary arteriography, exercise tolerance testing, and heart rate variability. Therefore, there were no qualitative signals for these outcomes.

Alpha-Linolenic Acid (ALA)

Qualitative signals were found for total cholesterol and LDL cholesterol, because pivotal new trials reported opposing findings. Two new trials of ALA found no effect on total cholesterol and LDL cholesterol, in contrast to the four trials in the original review which generally found small net increases in the lipids.

One pivotal trial was identified for fibrinogen, but the findings of this trial did not oppose the results of the original review. No pivotal trials were identified for the remaining cardiovascular risk factors. Therefore, there were no qualitative signals for these outcomes. However, among these outcomes, the original review included no evidence on the effect of ALA on seven outcomes (systolic and diastolic blood pressure, hemoglobin A1c, fasting glucose, fasting insulin, CRP, and carotid intima media thickness), and one or two new but small trials were found in the updated literature search. As a sensitivity analysis, these were categorized as having an A4 signal, that there were important changes in the effectiveness short of "opposing findings."

RAND Method

Fish Oil

The RAND method produced a signal indicating the probable need to update the original review for heart rate variability based on new trials and a minority of experts' opinion. The original review suggested no significant effect of fish oil on heart rate variability among healthy volunteers, but that heart rate variability may increase in patients with myocardial infarction. However, three of six new trials found that the fish oil group significantly improved heart rate variability. (Three of these studies were suggested by experts and were therefore not included in the Ottawa method.)

The RAND method showed a signal for the possible need to update total cholesterol and CRP based on new trials. The original review found that fish oil resulted in small nonsignificant net increases in total cholesterol and CRP. New studies, however, showed the fish oil groups had a significant decrease in total cholesterol and CRP. Based on a minority of experts' opinions, the RAND method found the possible need to update fasting glucose, systolic and diastolic blood pressure (in people with or without diabetes), fasting insulin, and coronary arteriography. One out of six experts indicated that the conclusions from the original review are out of date for systolic and diastolic blood pressure. However, one new systematic review[27] provided by the expert found very similar net changes as determined in the original review. Similarly, the findings on fasting glucose and fasting insulin were determined to be consistent overall between the original review and the new evidence. Lastly, one expert stated that the findings on coronary arteriography from the previous systematic review are out of date without providing any new evidence.

The RAND method did not produce any signal indicating the need for updating LDL or HDL cholesterol, triglycerides, lipoprotein (a), apolipoprotein A-1, apolipoprotein B, apolipoprotein B-100, LDL apolipoprotein B, hemoglobin A1c, fibrinogen, factor VII, factor VIII, von Willebrand factor, platelet aggregation, carotid intima media thickness, and exercise tolerance testing.

Alpha-Linolenic Acid (ALA)

The RAND method indicated a signal to possibly update total cholesterol, apolipoprotein A-1, and apolipoprotein B based on new studies, which had some evidence of significant decreases in these outcomes with ALA. In contrast, the original review found that ALA intake resulted in small or nonsignificant effects on these outcomes. Additionally, the RAND method demonstrated a signal for the possible update for LDL because the ALA groups showed net increases in LDL in the original review, but no effects on LDL from the updated search. We also concluded that there is a signal to probably update systolic and diastolic blood pressure, hemoglobin A1c, fasting glucose, fasting insulin, C-reactive protein, and carotid intima-media thickness because there were no ALA studies in the original review, but we found one or two new trials for these outcomes (three for C-reactive protein) from the updated search and the articles provided by the experts.

The RAND method demonstrated that the conclusions of the previous SR are still valid (based on new studies and experts' opinions) for HDL cholesterol, triglycerides, lipoprotein (a), apolipoprotein B-100, LDL apolipoprotein B, fibrinogen, factor VII, factor VIII, von Willebrand factor, platelet aggregation, coronary arteriography, exercise tolerance testing, and heart rate variability.

Summary of Discordant Results

Fish Oil

We obtained discordant results for 8 of 26 intermediate outcomes in studies of fish oil and cardiovascular risk factors when comparing between the RAND and Ottawa methods (Table 4; Appendix Table B4). The Ottawa method determined that there was no signal for systolic and diastolic blood pressure among diabetic patients, fasting insulin, CRP, coronary arteriography, and heart rate variability due to the absence of a pivotal trial. However, the RAND method found that results from the previous systematic review was possibly out of date for CRP based on new trials; probably out of date for heart rate variability based on expert opinion, one new trial found by the literature search, and three new trials from the experts; and possibly out of date for blood pressure in people with diabetes, fasting insulin, and coronary arteriography based on experts' opinion. However, the experts' opinions were not substantiated by new trials suggested by them for these latter outcomes. The literature search found no new studies on heart rate variability that provided a signal; however, one expert said the original report was out of date and provided three new trials to support that conclusion; these three trials were not considered for the Ottawa method.

For LDL and HDL, we found quantitative update signals using the Ottawa method due to one large Japanese study (n=18,645). This one outlier study changed the meta-analysis results for these intermediate outcomes. However, using the RAND method, we determined that results from the previous systematic review were still valid, though with a caveat about this one outlier study. We determined that this one outlier study, though extremely large, was not sufficient to contradict the 20 to 30 other (old and new) trials.

Table 4. Comparison of signals for updating the report on fish oil and cardiovascular risk factors

RAND	Ottawa Positive	Ottawa Negative	Total
Definitely out of date	0	0	0
Probably out of date	0	1	1
Possibly out of date	4	5	9
Still valid	2*	14	16
Total	**6**	**20**	**26**

* One very large trial had discordant results with almost all other trials. Our consensus was that this one outlier trial did not invalidate the original overall conclusions.

Alpha Linolenic Acid (ALA)

We obtained discordant results for 9 of 24 intermediate outcomes in studies of ALA and cardiovascular risk factors when comparing between the RAND and Ottawa methods (Table 5; Appendix Table B5). The original review included two ALA trials with data on apolipoproteins A-1 and B. The updated literature search found one new trial that may contradict the original review's trials; however, this trial was not large enough to be pivotal. Thus, by the RAND method, the original review is possibly out of date, but there was no signal using the Ottawa method.

There were no studies in the original review that assessed the effects of ALA on blood pressure, hemoglobin A1c, fasting glucose, fasting insulin, CRP, and carotid intima media thickness. Because the literature searches found one or two new trials for each of these outcomes (and an expert gave us a third CRP trial), the RAND method finds the previous conclusions "probably out of date." Since none of the new findings came from pivotal studies and no meta-analyses were performed previously for ALA on these outcomes, there is no signal using the Ottawa method.

However, if we apply the approach of assigning these as A4 signals with the Ottawa method, then these 7 outcomes are concordant and there are discordant results for only 2 of 24 intermediate outcomes in studies of ALA and cardiovascular risk factors.

Table 5. Comparison of signals for updating the report on ALA and cardiovascular risk factors

RAND	Ottawa Positive	Ottawa Negative	Total
Definitely out of date	0	0	0
Probably out of date	0 (7*)	7 (0*)	7
Possibly out of date	2	2	4
Still valid	0	13	13
Total	**2 (9*)**	**22 (15*)**	**24**

* For seven outcomes, the original report had no studies. The updated search found small new trials found for each. Thus, these could be interpreted as having an A4 signal (sensitivity analysis).

Comparison of Results Using the RAND and Ottawa Methods

We combined all the RAND signals, "definitely," "probably," and "possibly," out of date into a single category, "out of date" and compared the conclusions between methods within clinical topic area and across topics (Tables 6–10). The range of agreement varied from a kappa of 0.19 to "almost perfect" agreement with a kappa of 1.0. Overall across all 77 conclusions, agreement was classified as "fair."[13]

As discussed previously, many of the disagreements between methods were due to a situation where the original review had a Key Question with no evidence, and some evidence was identified in the update. In these situations, the RAND method produced a positive signal for updating and Ottawa's method produced a negative signal. Reclassifying these situations as agreement between the two methods yields much better estimates of agreement; for three of the

four conditions, agreement was “substantial” to “almost perfect,” and overall agreement was “substantial.”

Table 6. Overall comparison and kappa statistic for cognitive function

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	3	0	3
RAND Negative	0	2	2
Total	**3**	**2**	**5**

Kappa = 1.00

Table 7. Overall comparison and kappa statistic for cancer

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	1 (2*)	3 (2*)	4
RAND Negative	0	18	18
Total	**1**	**21**	**22**

Kappa = 0.36 (0.62*)
*Sensitivity analysis (see text)

Table 8. Overall comparison and kappa statistic for cardiovascular disease markers: fish oil

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	4	6	10
RAND Negative	2	14	16
Total	**6**	**20**	**26**

Kappa = 0.30

Table 9. Overall comparison and kappa statistic for cardiovascular disease markers: ALA

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	2 (9*)	9 (2*)	11
RAND Negative	0	13	13
Total	**2 (9*)**	**22 (15*)**	**24**

Kappa = 0.19 (0.83*)
*Sensitivity analysis (see text)

Table 10. Overall comparison and kappa statistic for all reviews

	Ottawa Positive	Ottawa Negative	Total
RAND Positive	10 (18*)	18 (10*)	28
RAND Negative	2	47	49
Total	**12**	**65**	**77**

Kappa = 0.36 (0.64*)
*Sensitivity analysis (see text)

Conclusions

In our primary analysis, overall agreement between methods ranged from "nonexistent" to "almost perfect." However, we judge our sensitivity analysis, which makes a reasonable modification to the Ottawa method, as being a more useful measure of agreement between the two methods. In our sensitivity analysis, agreement was "substantial" or better in three of the four conditions. Overall agreement between methods was "substantial." Many of the situations where the methods resulted in disparate recommendations were of the same general form, namely situations where "other" signals were triggered with the Ottawa method (but these signals were not considered as indicating that the review was out of date) whereas in RAND's method, the judgment was that the new evidence was sufficient to conclude that original was probably out of date. For example, for the finding related to the risk of developing one particular type of cancer, there were two existing cohorts with many thousands of subjects, neither reporting any association of fish or omega-3 fatty acids with incidence. To this evidence was added a new case control study (with 600 cases, but not meeting the pivotal article criteria) that reported an association. So, to increase the agreement between the two methods, either these kinds of "other" signals could be elevated to the level of a qualitative signal, or we would need to learn, using the RAND method, not to judge this kind of new data as being sufficient to consider the original conclusion as possibly out of date.

Our results support the hypothesis that either method can be used with confidence that it produces results that are about the same as the other method. However, stronger conclusions will await future replications of our study using different systematic reviews. A decision to update a systematic review might also be informed by the application of both methods, with the results compared to provide additional validation or to highlight areas of disagreement. Factors that may influence the choice of method, although not tested explicitly in the project could be any of the following:

- Level of expert engagement in the research topic (low levels favor Ottawa)
- Quality and variation in study designs found in the new evidence (low levels favor RAND, as Ottawa is designed with high-quality trials in mind)
- Desire for considering absolute levels of prior evidence, rather than only relative levels (high desire favors RAND, which allows more subjective application of updating signals; Ottawa's relative change signals do not take into the account whether you originally had 2 or 50 studies).
- Desire for a transparent, consistent signaling method that maximizes interrater reliability (high desire probably favors Ottawa, since signals have less flexibility)

In the process of conducting the two update signal methods in parallel, we ignored the findings of one method in evaluating the conclusions of the other. In particular, in conducting the qualitative and quantitative Ottawa methods, we did not include the new studies supplied to us by the domain experts. This artificial approach highlighted that there is not an either/or decision to be made as to which update signal method should be applied in the future. It seems logical that a hybrid approach may be most reasonable, using both input from subject matter experts and searching for pivotal trials or meta-analytic evidence of quantitative signals. Additionally, consideration should be given to the utility of other kinds of signals, such as the continuing use and importance of the original systematic review, the continuing use of the interventions assessed in the review, and whether there is an opportunity for the updating of the review to lead to a change in practice.

Additionally, although it would have been desirable to compare the resources involved in applying each method, this was not possible because each EPC was conducting the two methods simultaneously and the same Evidence-based Practice Center (EPC) staff were participating in both applications. Qualitatively, we note that the Ottawa approach alone would involve less work than the RAND method if one of the later randomized controlled trials (RCTs) that were assessed triggered a quantitative signal, as occurred with multiple outcomes for fish oil in the cardiovascular report and the additions of a very large (N=18,645) RCT from Japan. Conversely, when no quantitative signal is found even after adding all the seven new RCTs, as was seen in the assessment for the cancer review, the Ottawa method may take more work than the RAND method.

Further consideration should be given regarding what to conclude when a single expert votes that a topic is out of date and how to interpret experts' votes that a topic is outdated if no supporting evidence is provided. The cardiovascular review, in particular, had several instances where this was the case. For example, one of six experts stated that the original review's finding on blood pressure was out of date (fish oil supplementation results in small decreases in systolic and diastolic blood pressure). However, the one new article reporting on blood pressure was a systematic review[27] that had very similar conclusions to the EPC review. Similarly, the new evidence on fasting glucose and fasting insulin provided by the experts (two of whom stated that the review's conclusions were outdated) were consistent with the original review. And one expert said that the conclusions on coronary restenosis are outdated, but provided no supporting evidence. Notably, sticking to protocol, the Tufts EPC did not press the experts to provide supporting new evidence beyond the original request in the questionnaire. In the future, followup with the experts could be done easily. Analogously, further consideration needs to be given to the situation where a single trial provides a quantitative signal, where experts did not judge this new evidence to be a signal for updating, and the original EPC also judged the new evidence to be inconclusive in changing the original finding. This situation occurred in the fish oil and low-density lipoprotein–high-density lipoprotein outcomes with the addition of the above mentioned Japanese trial

The Tufts EPC had some difficulties implementing the RAND method when evaluating outcomes with sparse data. This difficulty was particularly evident for several cardiovascular risk factor outcomes of alpha-linolenic acid intake. Specifically, we had difficulty determining whether outcomes with zero to two studies in the original review were outdated when there were one or two new studies with small or nonsignificant results. We found that we came to different conclusions each time we reviewed the new evidence.

Finally, we cannot compare the predictive validity of the RAND and Ottawa methods, as no actual updates of the original reviews have been done. Such a predictive validity analysis will need to wait until reports assessed for signals are actually updated. When several updates have been performed on evidence reviews that have been analyzed for signals, it will be useful to analyze whether the Ottawa and RAND methods, or a combination of the two, accurately predict whether the updated systematic review will come to new conclusions compared to the original reviews. Additionally, two modifications to the Ottawa method are proposed for immediate use:

1. The extension of the qualitative signals criteria to conclude nontrial data for those Key Questions where the original review included non-trial evidence.
2. The designation of new evidence in a situation where the original review had no evidence as an A4 signal for updating.

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Appendix A. Search Strategies and Literature Flow

Table A1. Search terms to identify human studies of omega-3 FA and cancer for omega-3s and cancer

Search dates: 2003–May 25, 2010 and updated with the Nutrition and Cancer search on June 28, 2010

Tumor Incidence and Outcomes After Cancer Treatment
1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw,hw,rw.
8. eicosapenta?noic.tw,hw,rw.
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/ or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
29. (omega 3 or n 3).mp.
30. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
31. 29 and 30
32. 20 or 27 or 28 or 31
33. exp neoplasms/
34. (neoplasm$ or cancer$ or tumour$ or tumor$ or carcinoma$ or malignanc$).tw.
35. 33 or 34
36. 32 and 35

Journals used for the update search for the current report:

1. "Annals of internal medicine".jn. (25697)
2. Bmj.jn. (51943)
3. Jama.jn. (61018)
4. (Lancet or "lancet oncology").jn. (119986)
5. "New england journal of medicine".jn. (62986)
6. "American journal of clinical nutrition".jn. (16580)
7. "European jourSnal of clinical nutrition".jn. (4067)
8. "Jpen journal of parenteral & enteral nutrition".jn. (3426)
9. "American journal of public health".jn. (17424)
10. "American journal of epidemiology".jn. (10650)
11. "Bmc cancer".jn. (1930)

Table A2. Search terms to identify human studies of omega-3 FA and cognitive function

Search dates: 2003–May 28, 2010 but replaced with a later search that had no journal limits on June 28, 2010

Core search strategy (taken from original 2005 omega-3 report)
1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw
7. docosaheca?noic.tw,hw,rw
8. eicosapenta?noic.tw,hw,rw
9. alpha linolenic.tw,hw,rw.
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw,hw,rw
12. (mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multincenter study).pt.
23. random$.tw.
24.exp clinical trials/or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
29. (omega 3 or n 3).mp.
30. (polyunsaturated fat$ or pufa or dha or epa or long chain or long chain or lc$).mp.
31. 29 and 30
32. 20 or 27 or 28 or 31

Literature searches by disease category (taken from original 2005 omega-3 report)
Neurology
1. exp fatty acids, omega-3/v
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw.hw.rw.
8. elcosapenta?noic.tw.hw.rw.
9. alpha linolenic.tw.hw.rw
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw, hw,rw.
12. (Mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.

Table A2. Search terms to identify human studies of omega-3 FA and cognitive function (continued)

15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet $)).tw.
19. diet$ fatty acid$.tw.
20. or/1019
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. exp Aging/
29. Aged/
30. (aging or aged or geriatric$).tw.
31. or/28-30
32. 27 and 31
33. limit 27 to “all aged <65 and over>”
34. 32 or 33
35. exp Nervous System Disease
36. Alzheimer Disease/
37. exp Dementia/
38. parkinson disease/ or Parkinson disease, secondary/
39. parkinson disease/ or Parkinson disease, secondary/
40. exp Multiple Sclerosis /
41. exp Guillain-Barre Syndrome/
42. (alzheimer or parkinson or dementia or multiple sclerosis or guillain barre).tw.
43. (neurological disease$ or neurological disorder$).tw.
44. (neurological disease$ or neurological disorder$).tw.
45. exp Optic Nerve Diseases/
46. (myopathy or neuropathy).tw.
47. Cognition Disorders/
48. exp Cognition/
49. (cognition or cognitive).tw.
50. or/35-49
51. 27 and 50
52. exp fatty acids, omega-3/
53. fatty acids, essential/
54. Dietary Fats, Unsaturated/
55. linolenic acids/
56. exp fish oils/
57. (n 3 fatty acid$ or omega 3).tw.
58. docosahexa?noic.tw,hw,rw.
59. eicosapenta?noic.tw,hw,rw.
60. alpha linolenic.tw,hw,rw
61. (linolenate or cervonic or timnodonic).tw,hw,rw.
62. menhaden oil$.tw,hw,rw
63. ((Mediterranean adj diet$).tw.
64. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
65. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
66. (fish adj2 oil$).tw.
67. (cod liver oil$ or marine oil$ or marine fat$).tw.
68. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
69. (fish consumption or fish intake or (fish adj2 diet$)).tw.

Table A2. Search terms to identify human studies of omega-3 FA and cognitive function (continued)

70. diet$ fatty acid$.tw.
71. or/52-70
72. dietary fats/
73. (randomized controlled trials or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
74. random$.tw.
75. exp clinical trials/ or evaluation studies/
76. follow-up studies/ or prospective studies/
77. or/73-76
78. 72 and 77
79. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
80. (omega 3 or n 3).mp
81. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
82. 80 and 81
83. 71 or 78 or 79 or 82
84. 83 and 50
85. 84 not 51
86. 83 and 31
87. 86 not 34
88. limit 87 to “all aged <65 and over>

Journals used for the update search for the current report (for May 28, 2010 search):

1. Limit 62 to “core clinical journals (aim)” (132)
2. “American journal of epidemiology”.jn. (10671)
3. “European journal of clinical nutrition”.jn. (4082)
4. “Jpen journal of parenteral & enteral nutrition”.jn. (3426)
5. “BMC Geriatrics”.jn. (208)
6. “BMC Neurology”.jn. (315)
7. “Journal of neurology neurosurgery & psychiatry”.jn. (14631)

Table A3. Search terms to identify human studies of omega-3 FA and cardiovascular risk factors

Search dates: 2003–May 25, 2010

1	exp Fatty Acids, Omega-3/	11692
2	Fatty Acids, Essential/	3889
3	Dietary Fats, Unsaturated/	4121
4	Linolenic Acids/	1294
5	exp Fish Oils/	13938
6	(n 3 fatty acid$ or omega 3).tw.	7917
7	docosahexa?noic.tw,hw,rw.	7027
8	eicosapenta?noic.tw,hw,rw.	5784
9	(linolenate or cervonic or timnodonic).tw,hw,rw.	569
10	menhaden oil$.tw,hw,rw.	424
11	(mediterranean adj diet$).tw.	1123
12	((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.	4177
13	(walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.	19477
14	(fish adj2 oil$).tw.	5899
15	(cod liver oil$ or marine oil$ or marine fat$).tw.	908
16	(salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.	20386
17	(fish consumption or fish intake or (fish adj2 diet$)).tw.	3377
18	diet$ fatty acid$.tw.	1432
19	or/1-18	69765
20	dietary fats/	36196
21	(randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study or meta-analysis).pt.	760768
22	random$.tw.	508629
23	exp Clinical Trial/ or evaluation studies/	741476
24	follow-up studies/ or prospective studies/	641761
25	or/21-24	1520618
26	20 and 25	4833
27	(Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.	221
28	(omega 3 or n 3).mp.	42014
29	(polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.	98752
30	28 and 29	7974
31	19 or 26 or 27 or 30	74837
32	exp cardiovascular diseases/	1566882
33	Adhesion molecule expression.mp.	2085
34	Angiographic progression.mp.	101
35	Angioplast$.mp.	53559
36	(atherogen$ or antiartherogen$ or anti-artherogen$).mp.	20954
37	(arrhythmi$ or antiarrhythmi$ or anti-arrhythmi$).mp.	97013
38	endotheli$.mp.	229123
39	exp endothelium, vascular/	77800
40	Beta-thromboglobulin$.mp.	2639
41	Cardi$.mp.	813927
42	CHD.mp.	12497
43	Coronary.mp.	329921
44	Hypotens$.mp.	57619
45	Hypotriglyceridem$.mp.	252
46	heart disease$.mp.	153264
47	Myocardial infarct$.mp.	160737
48	Platelet adhesi$.mp.	9519
49	((postprandial or post-prandial) adj (lipemia or lipoprotein$)).mp.	705
50	Pulmonary Embol$.mp.	34171
51	Heart failure$.mp.	105125
52	Arteriosclerosi$.mp.	65056

Table A3. Search terms to identify human studies of omega-3 FA and cardiovascular risk factors (continued)

53	(cardioprotect$ or cardio-protect$).mp.	9318
54	Homocystine/	460
55	exp Homocysteine/	10895
56	homocyst$.mp.	17060
57	Cystine/	4964
58	Cystine.mp.	9344
59	exp Acute-Phase Proteins/	129564
60	Acute-Phase Protein$.mp.	7028
61	Acute-Phase Reaction/	2630
62	Acute-Phase React$.mp.	5479
63	exp Blood Coagulation Factor Inhibitors/	14042
64	exp Blood Coagulation Factors/	357239
65	blood coagulation factor$.mp.	12271
66	exp Cell Adhesion Molecules/	82827
67	cell adhesion molecule$.mp.	38891
68	exp Interleukins/	146546
69	interleukin$.mp.	196513
70	Lipid Peroxidation/	28060
71	Lipid Peroxidat$.mp.	42254
72	exp Hemostasis/	86937
73	hemosta$.mp.	37380
74	haemosta$.mp.	7481
75	exp Diagnostic Techniques, Cardiovascular/	571881
76	or/32-75	2978721
77	31 and 76	15703
78	limit 77 to yr="2003 - 2010"	6011
79	limit 78 to humans	4102
80	limit 78 to "in data review" or in process or "pubmed not medline"	241
81	79 or 80	4343

Journals used for the update search for the current report:

1. Bmj.jn. (51943)
2. Lancet.jn. (117602)
3. Jama.jn. (61018)
4. “New england journal of medicine”.jn. (62986)
5. “Annals of internal medicine”.jn. (25697)
6. “American journal of clinical nutrition”.jn. (16580)
7. “American journal of cardiology”.jn. (30501)
8. “Arteriosclerosis thrombosis and vascular biology”.jn. (5909)
9. Atherosclerosis.jn. (9082)
10. Atherosclerosis supplements.jn. (165)
11. “Diabetes care”.jn. (12772)
12. “European journal of clinical nutrition”.jn. (4067)
13. Lipids.jn. (6468)
14. “Thrombosis and haemostasis”.jn. (10916)
15. “Thrombosis research”.jn. (9447)
16. “Circulation research”.jn. (13414)
17. “Cardiovascular research”.jn. (8630)
18. “European heart journal”.jn. (11372)
19. “Bmc cardiovascular disorders”.jn. (297)

Literature Flow Diagrams

Figure A1. Literature flow diagram for cognitive functions (used for both the RAND and Ottawa methods)

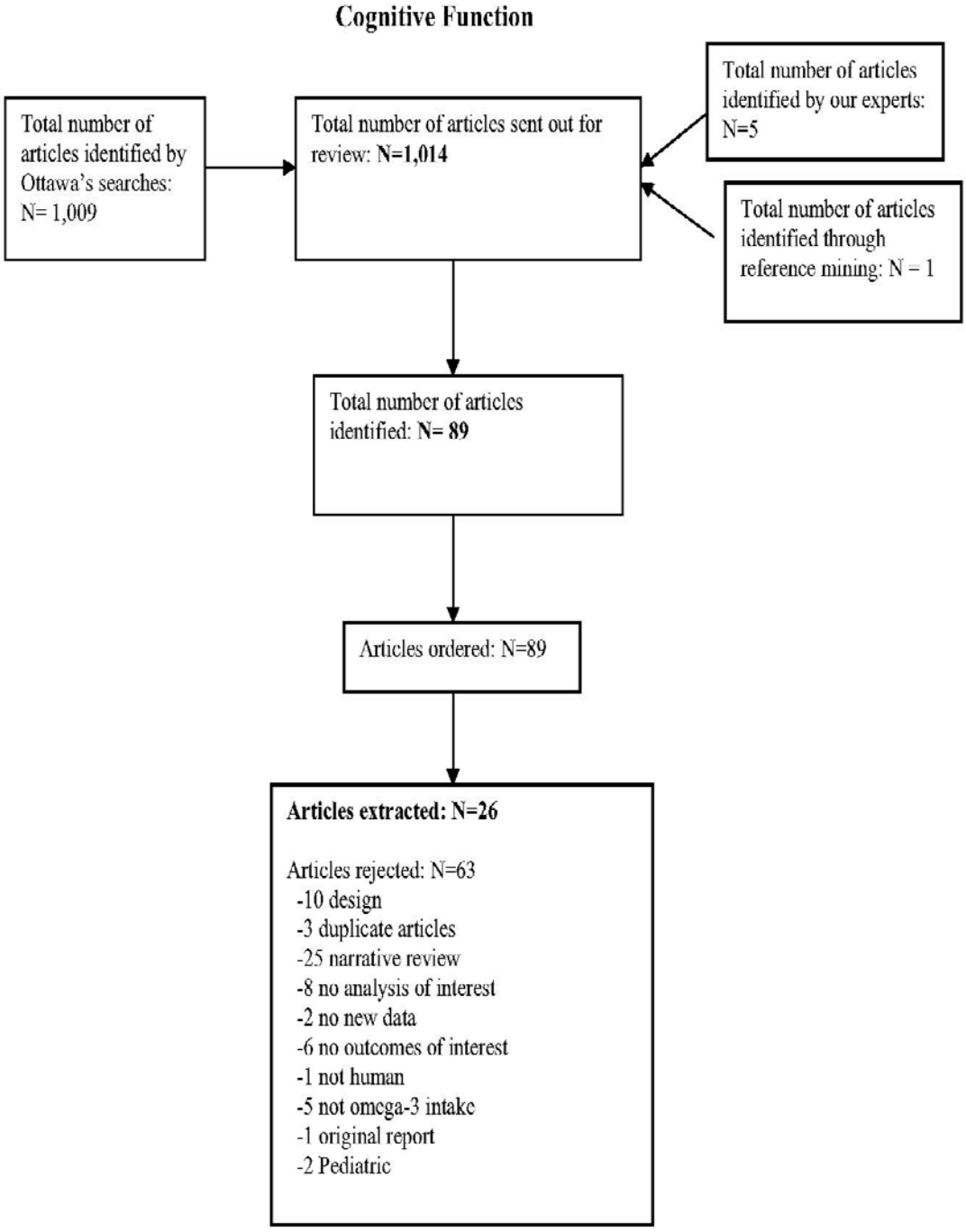


Figure A2. Literature flow diagram for cancer (used for both the RAND and Ottawa methods)

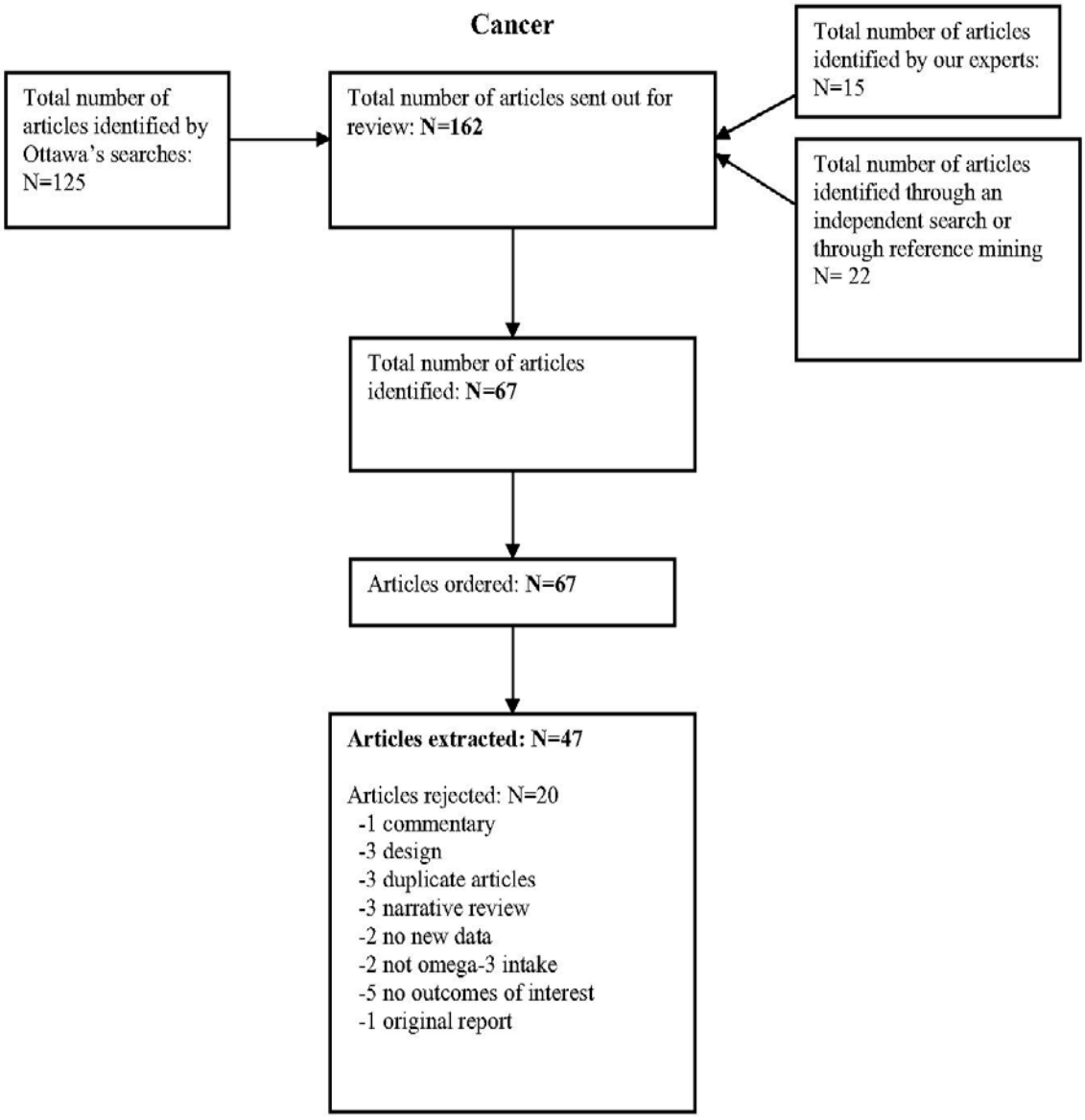
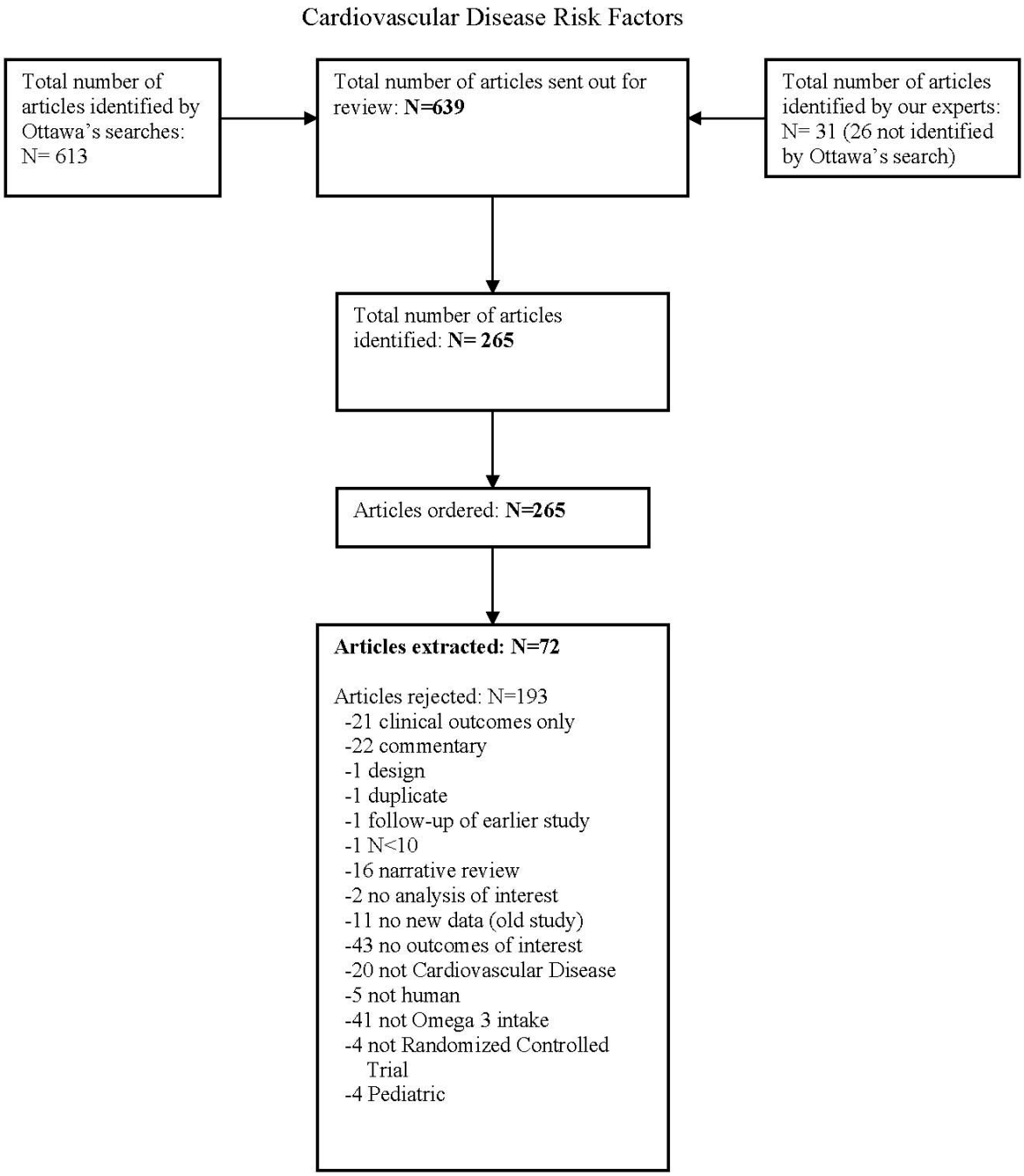


Figure A3. Literature flow diagram for cardiovascular disease factors (used for both the RAND and Ottawa methods)



Appendix B. Summary Tables

Cognitive Function

Table B1. Updating effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological disease

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Key Question 1: What is the evidence that omega-3 FA play a role in maintaining cognitive function in normal aging?				
Only one study (n=818, all men) that met inclusion criteria assessed the role of omega-3 FA in maintaining cognitive function. Fish consumption was only weakly associated with a reduced risk of cognitive impairment and had no association with cognitive decline. Omega-3 FA consumption was not associated with either outcome.	The evidence base is much larger than before, and it includes RCTs and measures of plasma biomarkers that are related to omega-3 FA intake. The updated search found 13 relevant studies (4 RCTs, 9 prospective cohort studies) representing a total of n=15,739 unique subjects. Six studies showed no or weak positive associations between cognitive decline or function and omega-3 intake or related plasma biomarkers. The remaining seven studies found a positive effect of increased fish/omega-3 intake or related plasma biomarkers on cognitive function or risk of cognitive decline. Four studies showed stronger protective effects for those with low depression, hypertension, dyslipidemia, and APOE-e4 noncarrier status. One study (Van Gelder, 2007) evaluated the same population as the 1997 study included in the prior report, using a longer followup period and refined dietary intake variables. The 2007 study arrived upon different conclusions, finding a strong inverse association between no fish intake and EPA+DHA intake with cognitive decline – a relationship which was not significant in the 1997 study.	Three experts recommended additional articles, which were screened and included if they met inclusion criteria. Other than citing those studies' findings, experts did not provide detailed commentary about whether they felt the evidence had changed. One expert believed the conclusion is strengthened based on recent evidence.	The original conclusion is probably out of date and this portion of the CER may need updating based on substantial new data, including different conclusions about the same study group described in the prior report.	A4, important change in effectiveness short of opposing findings, and A6, clinically important caveat. Both signals are from a pivotal study, defined by sample size of n=7,814, but in a specialty medical journal rather than a major general journal. Three other signals met: increase in total number of trials by $\geq$ 50%, increase in total number of subjects by $\geq$ 50%, publication of new trial with n $\geq$ 3 times the size of the previous largest trial.

Table B1. Updating effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological disease (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Key Question 2: What is the evidence that omega-3 FA affect the incidence of dementia including Alzheimer's disease?				
Three studies (combined n=7,323) evaluated the effect of omega-3 FA on the incidence of dementia, relative to fish consumption; one study also assessed risk relative to total omega-3 FA consumption, and relative to consumption of ALA, EPA, and DHA, individually. Fish intake was associated with a significant reduction in the incidence of non-Alzheimer's dementia in one study; and a significantly reduced risk of Alzheimer's dementia in one study. Intake of total omega-3 FA and DHA alone (but not ALA or EPA alone) were associated with a significant reduction in the incidence of Alzheimer's.	The evidence base is much larger than before, and it includes measures of plasma biomarkers that are related to omega-3 FA intake. The updated search found six relevant studies (all prospective cohort studies) representing a total of n=17,275 unique subjects. Two studies found no relationship between omega-3 intake (including total and EPA or DHA alone) or related plasma biomarkers and incidence of dementia or Alzheimer's. Four studies found positive effects of these diet and plasma variables and reduced risk of developing dementia or Alzheimer's. Studies that measured APOE-e4 carrier status found mixed results about whether noncarrier status was significantly protective. One study (Devore, 2009) evaluated the same population as a 1997 study included in the prior report, using a longer follow-up period (10 years vs. 2 years). The 2007 study arrived upon different conclusions, finding no significant relationship between increased fish intake and reduced risk of dementia.	Three experts recommended additional articles, which were screened and included if they met inclusion criteria. One commented that "several clinical trials investigating the effects of omega-3-fatty acid supplementation in AD have been completed and all failed." Another expert noted, "there are some small RCTs that suggest benefit but no definitive trial that would result in recommendations to use omega-3 to prevent or delay cognitive decline.".	The original conclusion is probably out of date and this portion of the CER may need updating based on substantial new data, including different conclusions about the same study group described in the prior report.	A4, important change in effectiveness short of opposing findings and A6, clinically important caveat. The signals are from several non-pivotal studies, as no studies surpassed the previous largest sample size by a factor of 3. Two other signals met: increase in total number of trials by $\geq$ 50%, increase in total number of subjects by $\geq$ 50%

Table B1. Updating effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological disease (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Key Question 3: What is the evidence that omega-3 FA are effective in the treatment of dementia including Alzheimer's disease?				
Only one study (n=20) assessed the effects of omega-3 FA for the treatment of dementia. DHA resulted in a small improvement in scores on a dementia rating scale.	The evidence base is stronger than before. The updated search found 2 relevant studies (both RCTs) representing a total of n=209 unique subjects. One of these studies found a positive effect of n-3 PUFA supplementation on one measure of global cognitive function for younger subjects with cognitive impairment, but null effects for several other cognitive measures. The other study found no effect for subjects with mild to moderate Alzheimer's.	One expert commented that "evidence continues to be very weak; no substance has been shown to improve outcomes once the disease is clinically evident." Another expert responded that "several clinical trials investigating the effects of omega-3 FA supplementation in AD have been completed and all failed to demonstrate its efficacy in the treatment of AD. However, these trials produced intriguing data suggesting that the beneficial effects of omega-3 FA supplementation may depend on the stage of disease, other dietary mediators, and APOE-e4 status."	The original conclusion is probably out of date and this portion of the CER may need updating based on substantial new data.	A4, important changes in effectiveness short of opposing findings. This signal is from a pivotal trial defined by sample size of n=174, but in a specialty medical journal rather than a major general journal. Three other signals met: increase in total number of trials by $\geq$ 50%, increase in total number of subjects by $\geq$ 50%, publication of new trial with n $\geq$ 3 times the size of the previous largest trial.

Table B1. Updating effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological disease (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Key Question 4: What is the evidence that omega-3 FA affect the incidence of OTHER neurological diseases?				
Four studies (combined n=136,202) addressed the association of omega-3 FA consumption with risk or incidence of particular neurological diseases other than dementia. Two studies that assessed the association between omega-3 FA intake and the incidence of multiple sclerosis found no significant effects, although one study found a reduced risk with fish consumption in women. The one study that assessed the association between omega-3 FA consumption and the risk for Parkinson's disease found no significant association for fish, ALA, EPA, or DHA. The one study that assessed the association between maternal omega-3 FA consumption and the risk of giving birth to a child with cerebral palsy found that eating fish once a week throughout pregnancy was associated with a lower risk.	The prior evidence base was strong, and relatively little new evidence has emerged. No new studies address multiple sclerosis or cerebral palsy. The updated search found two relevant studies (one prospective cohort and one case-control study) representing a total of n=5906 unique subjects, measuring incidence of Parkinson's disease. One study found a positive, but weak/inconsistent effect of total omega-3 PUFA and ALA intake on lower incidence of Parkinson's disease, but total unsaturated fats appeared to be more important. The other study found no significant associations between intake of total omega-3 FA, ALA, EPA, or DHA and incidence of Parkinson's disease.	No relevant expert feedback.	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No qualitative signals. One other signal met: increase in total number of trials by $\geq$ 50%

Table B1. Updating effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological disease (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Key Question 5: What is the evidence that omega-3 FA prevent the progression of multiple sclerosis?				
Three studies (combined n=340) reported on the side effects of omega-3 FA intake on the progression of multiple sclerosis. In one study, treatment with an omega-3 FA supplement had no effect on disability or relapse rates. However, two other studies reported a significant reduction in disability and one reported improvement on an index of disease progression.	Relatively little new evidence has emerged. The updated search found one RCT study (n=27). The study found weak evidence of a positive effect of fish oil supplementation on MS quality of life and outcome measures, although treatment subjects were also subject to a lower-fat dietary intervention (vs. moderate fat in the placebo arm), which may partially explain the results.	One expert commented that 1–2 papers support the prior conclusion, but was unsure how recent those papers were relative to our original report. One expert recommended an additional systematic review, which was reference mined, but did not provide any new articles that were not already found. The expert reiterated the review's conclusions, which were that PUFAs did not have a significant effect on disease progression for MS.	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No qualitative signals. No other signals.
Are there new data that could inform the Key Questions that might not be addressed in the conclusions? **General expert responses:** #2 It seems that more detailed analyses are able to detect subgroups of patients that may be more responsive to PUFA supplementation on the basis of APOE4 status and the disease stage. #3 Given the extensive topic areas, I would need an updated search of the literature in order to answer these questions correctly. If you have this type of search available for me to review, I would be glad to be more specific in my responses. Otherwise I do not have specific references to add and my responses at this point are that I do not know if there is evidence to invalidate the findings. **Additional Key Questions:** There are new data that could inform a Key Question that is related to, but not addressed by existing Key Questions. Two new RCT studies (combined n=350) were found that evaluate the effect of omega-3 FA on treatment of Huntington Disease. One study found that ethyl-EPA supplementation did not improve motor skills for patients with HD. The other study found that MRI scans showing brain volume changes and cerebral atrophy were improved in patients treated with ethyl-EPA, noting that no other drug tested in Huntington Disease has shown this effect.				

AD = Alzheimer's disease; ALA = alpha linolenic acid; CER = comparative effectiveness review; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FA = fatty acid; PUFA = polyunsaturated fatty acid

Cancer Risk and Response to Treatment

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Key Question 1: Effect on tumor incidence **Key Question 1A: What is the evidence that omega-3 fatty acids reduce the incidence of tumors (in humans)? For what type of tumors?**				
All cancers, the 2005 report found that omega-3 fatty acids do not appear to decrease overall cancer risk based on finding of no effect for most types of cancer	The updated search found 2 relevant studies (2 prospective cohort studies) representing a total of n=74,701 unique participants). Both studies showed no association between intake of fish, fatty fish, DHA, or EPA and overall incidence of cancer.	These responses pertain to cancer in general as well as specific types of cancer: #2 This conclusion is almost certainly still supported by the evidence #4 Does not know if the conclusion is still supported by the evidence #6 Cohort studies might provide new evidence that will change the conclusions regarding colorectal, breast, and other cancers Engeset Eur J Cancer Prev 2009 Feb;18(1):69–75. Dietary patterns and risk of cancer of various sites in the Norwegian European Prospective Investigation into Cancer and Nutrition cohort: the Norwegian Women and Cancer study	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal
Aerodigestive Cancer Original report identified one study (8,006 Japanese-American men) that showed no significant effect of fish on the incidence of aerodigestive cancer (Honolulu Heart Program [Chyou 1995])	No new studies identified		The original conclusion is still valid and this portion of the CER does not need updating based on absence of new data.	No signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Bladder Cancer Original report identified one study (8,006 Japanese-American men) that showed no significant effect of fish on the incidence of bladder cancer (Honolulu Heart Program [Chyou 1995])	No new studies identified		The original conclusion is still valid and this portion of the CER does not need updating based on absence of new data.	No signal
Breast Cancer Original report identified 7 studies (6 cohorts) Fish consumption (4 studies): 1 study found increased risk in highest vs. lowest quartile of fish intake (n=29,875 Caucasian women); other three studies found no effect (n=120,000; 14,729; 121,700) Total and marine n-3 FA (1 study): Highest quartile of marine n-3s had lower risk than women in lowest quartile (n=63,257 Asian women) Specific n-3s (1 study): Highest quartile of ALA had lower risk than lowest quartile (n=62,573 men and women[# women unknown]) No evidence for fish oil, total omega-3s, DHA, or EPA	8 new studies (>100% increase in number of studies) with more than 50% increase in number of participants, total. Fatty fish: Contradictory findings with 1 pivotal study (by size) showing potential detrimental effect Total fish: contradictory results in two studies Total omega-3 FA: Inconsistent results, with three studies showing decreased risk and one showing no effect Marine omega-3 FA: Inconsistent results across two studies EPA: slightly decreased risk in three studies DHA: slightly decreased risk in one study ALA: Inconsistent effect on risk in one study, depending on food source Erythrocyte omega-3 FA concentrations: no effect.	#6 See Wakai Cancer Sci. 2005 Sep;96(9):590-9. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan Engeset D Int J Cancer 2006 Jul 1;119(1):175–182. Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC). Kim J BMC Cancer. 2009 Jun 30;9:216. Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study. Brasky TM. Cancer Epidemiology Biomarkers and Prevention 2010. 19(7): 1696–1708. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) cohort	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Breast Cancer (cont.)		Gago-Dominguez M Br J Cancer 2003 Nov 3;89(9):1686–1692. Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. [pre-Omega 3s-1?]		
Colorectal Cancer Original report identified 6 studies (6 cohorts): Fish consumption (4 studies): 1 study found decreased risk in highest vs. lowest quartile of fish intake in 1 study (n=14,727 women); other three studies found no effect (n=47,949 men; 3,111 men and women; 88,751 women) Total n-3 FA (1 study): Highest quartile of n-3s had non-significantly lower risk than women in lowest quartile (n=35,215 Caucasian women) Specific n-3s (1 study): No difference for any n-3 (n=61,483 Caucasian women)	eight new studies with more than 50% increase in number of participants: Total fish: inconsistent findings across four studies Marine sources of omega-3 FA: Opposing findings across three studies Total omega-3 FA: Inconsistent findings across three studies ALA: Opposing findings in men and women in one study EPA+DHA: dose dependent decrease in one study DHA: Decrease in men in one study	#5 (and #7) No clear effects of fish consumption on risk markers of colorectal cancer, confirming findings of the original report: published references: European J Clinical Nutrition 2009; 63(11):1353; Carcinogenesis 2010;31(6):1087; J Nutr 2010;140(2):371). #6 Norat, J Natl Cancer Inst.2005 Jun 15;97(12):906–916. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition Kojima M Serum levels of polyunsaturated fatty acids and risk of colorectal cancer: a prospective study. (ref not included) Thiébaut AC Int J Cancer.2009 Feb 15;124(4):924–931. Dietary intakes of omega-6 and omega-3 polyunsaturated fatty acids and the risk of	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Colorectal Cancer (cont.)		breast cancer. Chavarro JE Am J Clin Nutr 2008 Nov;88(5):1297–1303. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. Butler LM Int J Cancer 2009 Feb 1;124(3):678–686. Marine n-3 and saturated fatty acids in relation to risk of colorectal cancer in Singapore Chinese: a prospective study. Hall MN Cancer Epidemiol Biomarkers Prev 2008 May;17(5):1136–1143. A 22-year prospective study of fish, n-3 fatty acid intake, and colorectal cancer risk in men. Hall MN Cancer Epidemiol Biomarkers Prev 2007 Feb;16(2):314–321. Blood levels of long-chain polyunsaturated fatty acids, aspirin, and the risk of colorectal cancer. Daniel CR Cancer Epidemiol Biomarkers Prev 2009 Feb;18(2):516–525. Epub 2009 Feb 3. Dietary intake of omega-6 and omega-3 fatty acids and risk of colorectal cancer in a prospective cohort of U.S. men and women.		

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Lung Cancer: Original report identified three studies (three cohorts) that assessed effect of n-3s on incidence and one that assessed effect on mortality One study found decreased risk with highest vs. lowest tertile fish intake; other studies found no effect of higher fish consumption on incidence or death	No new findings		The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal
Lymphoma: Original report identified 2 studies (2 cohorts) on incidence of non-Hodgkins lymphoma (NHL) Fish intake:1 study found no effect of increasing fish consumption (35,156 women) Total n-3s: 1 study found no effect of increasing intake of omega-3s (as % total caloric intake) (88,410 women)	1 new case-control study (614 cases) reported significant effect of total and marine omega-3 FA on incidence of NHL		The original conclusion is probably out of date and this portion of the CER may need updating based on new data from one large observational study	No signal
Ovarian Cancer Original report identified one study that assessed the effect of various kinds of fat, including n-3s, on incidence and found no effect	No new studies		The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Pancreatic Cancer Original report identified 2 studies (2 cohorts) Fish consumption (1 study): no significant effect of fish consumption (27,111 men) Total n-3 consumption (1 study): no effect of n-3s ALA (2 studies): no effect of ALA (27,111 men; 88,802 women)	No new studies		The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal
Prostate Cancer Original report identified 7 studies (5 cohorts) Fish consumption (4 studies): 1 study showed inverse effect (6,272 men); one study showed positive effect (14,000 Seventh-day Adventists); other two studies (total 56,763) showed no effect Marine omega-3s (1 study): no effect found (47,855 health professionals) DHA and EPA (two studies): no effects seen (approx. 108,000) ALA (3 studies): increased risk for advanced cancer but not overall (47,866) in one study; no significant effect in the other (58,279) (data missing for 3rd)	9 new studies (7 cohorts) and MA. Total fish: findings inconsistent across 3 studies Fatty fish: no effect in 1 study Marine omega-3 FA (from fatty fish): decreased risk in 1 study Total omega-3 FA: trend toward ↓ risk in Caucasian and Latino men but no effect in others in 1 study ALA: MA showed inconsistent findings among 16 studies; inconsistent findings across 4 other studies EPA: inconsistent findings across 3 studies DHA: inconsistent findings across 2 studies Findings remain contradictory with some showing positive, some negative, and some no association	#6 See: Pham TM. Public Health Nutr 2009 May;12(5):609–613. Epub 2008 Jul 29. Fish intake and the risk of fatal prostate cancer: findings from a cohort study in Japan. Leitzmann 2004 Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. Am J Clin Nutr 2004; 80(1):204–216 [in original report]	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Renal Cancer No studies in original report	Two new studies, one in a pivotal journal Baltic herring: ↑risk but nonrepresentative population (Alpha-Tocopherol Beta-Carotene Cancer (ATBC) Prevention Study of smokers Cohort study in pivotal journal: Fatty fish: ↓↓ risk Lean and other fish: no effect seen		The original conclusion is probably out of date and this portion of the CER may need updating based on new data from one large observational study in pivotal journal	A4: One pivotal study showed strong benefit A6: One large trial showed evidence of potential harm for smokers
Skin Cancer Original report found 1 study that looked only at basal cell carcinoma (BCC). Highest n-3 consumption associated with small but significantly increased risk of BCC relative to lowest quartile. (43,217 health professionals)	1 new study on actinic keratosis Fatty fish: ↓risk for appearance of actinic keratoses compared with lower intakes		The original conclusion is probably out of date and this portion of the CER may need updating based on new data from one large observational study	No signal
Stomach Cancer Original report identified one study that assessed risk relative to fish consumption and found no effect.	No new studies		The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Effect on Tumor Incidence **Key Question 1b: If omega-3 fatty acids influence the incidence of tumors, is there an inverse relationship with intake?**				
Data were insufficient to permit assessment of a dose-response relationship. Original report identified the following dose effects Breast cancer: dose effects for marine n-3s and ALA; no dose effects for fish, total n-3s, DHA, EPA Colorectal cancer: dose effects tested but not observed Lung cancer: study that reported reduced risk of CA reported dose effect Lymphoma: dose effects tested but not observed Ovarian cancer: no dose effects observed Pancreatic cancer: dose effects tested but not observed Prostate cancer: Dose effects tested in all seven studies. Dose effects seen for fish in two of four studies, but in opposite directions. Dose effects seen for ALA in two studies but in opposite directions. No dose effect seen for EPA, DHA, total n-3s. Skin cancer: Study found increased risk with increasing dose. Stomach cancer: dose response assessed but not seen	Two new case-control studies showed a dose-response relationship: one showed a relationship for EPA, DHA, EPA+DHA and ALA with colorectal cancer; the other showed a weak relationship for total omega-3 FA and colorectal cancer	#2 This conclusion is almost certainly still supported by the evidence #4 Does not know if the conclusion is still supported by the evidence #6 See articles cited for KQ1a if positive relationship found	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Effect on Tumor Incidence **Key Question 1c: Is there a temporal relationship with intake?**				
Data were insufficient to permit assessment of a temporal relationship	No new studies were identified that addressed this question.	#4 Does not know if the conclusion is still supported by the evidence #6 See articles cited for KQ1a if positive relationship found	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal
Key Question 1d: If omega-3 fatty acids influence the incidence of tumors, what is the evidence that genes involved in omega-3 fatty acid transport or metabolism influence the magnitude or direction of the influence on tumor incidence?				
No studies were identified that investigated the role of omega-3 fatty acid transport or metabolism genes in any putative effect of omega-3 fatty acids on tumor incidence	One new study found a significant interaction with small nuclear polymorphism (SNP) in COX-2 gene (key enzyme in eicosanoid synthesis, over-expressed in prostate cancer tissue) but not with four other SNPs	#2 This conclusion is almost certainly still supported by the evidence #4 Does not know if the conclusion is still supported by the evidence #6 Does not believe there is any change in the evidence	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal
Key Question 1e: What is the evidence that the response to omega-3 fatty acids is independent of the intake of antioxidants such as vitamin E or other bioactive food components?				
No studies were identified that allowed this question to be answered	No new studies were identified that answered this question	#2 This conclusion is almost certainly still supported by the evidence #4 Does not know if the conclusion is still supported by the evidence #6 Does not believe there is any change in the evidence	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal
Key Question 1f: What is the evidence that the response is modified by the state of the immune system?				
No studies were identified that examined the possible modification of the effect of omega-3 fatty acids by immune status.	No new studies were identified that answered this question	#2 This conclusion is almost certainly still supported by the evidence #4 Does not know if the conclusion is still supported by the evidence	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Key Question 2: Effects on Clinical Outcomes after Cancer Treatment **Key Question 2a: What is the evidence that omega-3 fatty acids alter the effects of cancer treatment on malignant tumors and clinical outcomes after cancer treatments?**				
We identified 19 studies from which the effect of omega-3 fatty acids on clinical outcomes after cancer therapy could be ascertained, all of which pertained to patients who had undergone cancer surgery for upper gastrointestinal malignancies. We did not identify any studies that assessed the effects of omega-3 fatty acids on clinical outcomes after chemotherapy or radiation surgery. Among the identified studies, 14 described the effect on post-operative complications, 13 on hospital length of stay, 10 on mortality, 11 on nutrition and three on weight. In pooled analyses, omega-3 fatty acids had no effect compared to placebo on post-operative complications, hospital length of stay, or mortality. With the exception of one study that demonstrated higher mean nitrogen intake for subjects treated with omega-3 fatty acids relative to placebo, no significant effect on nutrition or weight loss was observed.	2 new Phase II trials assessed response to chemotherapy: both identified improved outcomes (1 for DHA and 1 for EPA) but recommended RCTs 10 new studies assessed the response to surgery: Postoperative complication rate: Enteral formula supplemented with EPA, DHA+EPA, omega-3 FA+arg, high ratio omega-3 FA to omega-6 FA: no effect found Fish oil: inconsistent effects across 2 studies Impact enteral nutrition formula: Decreased post-op complications Length of stay: Fish oil: inconsistent effects across 2 studies Impact: 2 studies found decrease Weight gain/loss: inconsistent effects across 3 studies Nutritional parameters: inconsistent effects across 4 studies	#2 The substantial literature on Impact and other immune-enhancing diets which contain fish oil along with other immune-enhancing compounds which on meta-analysis has shown benefits for length of stay and infections in postoperative patients #4 Does not know if the conclusion is still supported by the evidence. #6 The following studies should be added: Bougnoux P Br J Cancer 2009 Dec 15;101(12):1978–1985. Epub 2009 Nov 17. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. Liang B World J Gastroenterol 2008 Apr 21;14(15):2434–2439. Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients.	Chemotherapy: The original conclusion is definitely out of date and this portion of the CER needs updating based on new data from 2 Phase II trials. Postoperative recovery: The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	Chemotherapy: No signal Postoperative recovery, length of hospital stay, and nutritional status: No quantitative or qualitative signal

Table B2. Updating effects of omega-3 fatty acids on cancer risk and response to treatment (continued)

Conclusions in 2005 Report	RAND Literature Search	Expert Opinion	Conclusion from RAND EPC	Ottawa Update Signals
Key Question 2b: What is the evidence that the response to omega-3 fatty acids is independent of the intake of antioxidants such as vitamin E or other bioactive food components?				
No studies were identified that allowed this question to be answered.	No studies were identified that allowed this question to be answered.	#2 This conclusion is almost certainly still supported by the evidence #4 Does not know if the conclusion is still supported by the evidence	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal
Key Question 2c: What is the evidence that the response is modified by the state of the immune system?				
No studies were identified that examined the possible modification of the effect of omega-3 fatty acids on clinical outcomes by immune status.	No studies were identified that allowed this question to be answered.	#2 This conclusion is almost certainly still supported by the evidence #4 Does not know if the conclusion is still supported by the evidence	The original conclusion is still valid and this portion of the CER does not need updating based on insufficient new data.	No signal
Are there new data that could inform the Key Questions that might not be addressed in the conclusions?				
		#1 There is no new evidence that would alter the conclusions or require re-review. #3 Given the extensive topic areas, I would need an updated search of the literature in order to answer these questions correctly. If you have this type of search available for me to review, I would be glad to be more specific in my responses. Otherwise I do not have specific references to add and my responses at this point are that I do not know if there is evidence to invalidate the findings.		

ALA = alpha linolenic acid; arg = arginine; BCC = basal cell carcinoma, CER = comparative effectiveness review; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FA = fatty acid; n-3 = omega-3; PUFA = polyunsaturated fatty acid

Cardiovascular Disease Risk Factors

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Original Key Questions (abbreviated and re-phrased) *What is the effect of omega-3 fatty acids (EPA, DHA, ALA; fish; supplements or dietary) on cardiovascular risk factors and intermediate markers of cardiovascular disease (see list of outcomes below)?* *How do the effects differ by* ● *Dose* ● *Duration of intake* ● *Specific omega-3 fatty acid (or their ratios)* ● *Source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, flax seed supplement)* ● *Ratio of omega-6 to omega-3 fatty acids* ● *Population (men, pre-menopausal women, post-menopausal women, different age groups)* ● *Baseline dietary intake of omega-3 fatty acids* ● *Presence of potential confounders* ○ *Body mass index* ○ *Blood pressure* ○ *Medications* ● *Pre-existing conditions* ○ *Diabetes* ○ *Hypertension* ○ *Hyperlipidemia* ○ *Known cardiovascular disease* *Are the effects sustained after the intervention or exposure stops?*				

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Total cholesterol (TC)				
23 RCTs (20 FO, 4 ALA) (N≥60 [parallel design], N≥40 [crossover]) 1. The studies "were heterogeneous, but mostly found small (0% to 6%), non-significant net increases in level of [total cholesterol]." 2. "The effect of plant oils (ALA) on [TC] was possibly weaker but similar to the effect of marine oils." 3. 19 fish oil (FO) studies: Summary net effect 0 (95% CI -1, +2) mg/dL [μ=0.4257; SE=0.9537]; Higher mean baseline TC associated with larger net decrease in TC.[24] 4. 5 ALA studies: Range of net effects -1, +13 mg/dL[24] 5. No clear evidence of different effects in different populations 6. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of n-3 FA 7. No difference in effect seen across 5 weeks and 2 years of exposure. 8. No evidence on sustainment of effect.	From our literature search: 12 RCTs (9 FO, 1 n-3 FA rich diet, 2 ALA) From experts: 3 RCTs (3 FO) 1. 1 RCT from literature search and 2 RCTs from experts found a significant net decrease in TC, but other studies showed no significant effect. 2. No new data were found. 3. 9 fish oil studies from search: no sig. effect on TC in 8 studies; 3 fish oil studies from experts: no sig. effect in 1 study 1 n-3 FA rich diet (from literature search): no sig. effect on TC 4. 2 ALA studies (from literature search): no sig. effect 5. 1 fish oil study ● No difference with normoglycemia or impaired glucose metabolism ● For high-risk group (TG ≥150 mg/dL and HDL-C <40 mg/dL), no sig effect on TC. 6. 2 fish oil studies, **no clear evidence** of a **dose effect** 7-8. No new data were found.	Five of the six experts stated that the findings of the original report are almost or certainly still supported by the evidence; one was undecided.	● FO: Possibly out of date (based on new trials) ● ALA: Possibly out of date (based on new trials)	**Quantitative:** FO: Change in statistical significance, NS to Sig (B1) ALA: N/A **Qualitative:** FO: Opposing findings (A1) ALA: Opposing findings (A1)

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
LDL cholesterol				
15 RCTs (14 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 9. "The effect of omega-3 fatty acid consumption was fairly uniform across studies. Most found a net increase in LDL with treatment." 10. "The effect of plant oils (ALA) on [LDL] was possibly weaker but similar to the effect of marine oils." 11. 13 fish oil studies: Summary net effect +6 (95% CI +3, +8) mg/dL[24] 12. 3 ALA studies: Range of net effects -2, +3 mg/dL[24] 13. No clear evidence of different effects in different populations 14. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of n-3 FA 15. No difference in effect seen across 8 weeks and 2 years of exposure. 16. No evidence on sustainment of effect.	From update literature search: 10 RCTs (6 FO, 2 n-3 FA rich diet, 2 ALA) From experts: 3 RCTs (3 FO) 9. Most of the studies showed no significant effects on LDL. 10. No new data were found. 11. 6 fish oil studies (from literature search): sig effect in 1 study 3 fish oil studies (from experts): sig increase in 1 study 2 n-3 FA rich diet (from literature search): no sig. effect 12. 2 ALA studies: no sig. effect 13. 2 fish oil studies ● 1 study: No difference with normoglycemia, impaired glucose, or hypertriglyceridemia ● 1 study: The baseline LDL cholesterol had a significant interaction with n-3 treatment for the LDL cholesterol response (p=0.022). 14. 2 fish oil studies, **no clear evidence** of a **dose effect** 15-16. No new data	Five of the six experts stated that the findings of the original report are almost or certainly still supported by the evidence; one was undecided. One agreed, adding, "The question has come up as to whether there may be differences in LDL between EPA and DHA, such that EPA lowers LDL whereas DHA raises LDL. I have not seen published data in this regard but it may be worth assessing." One also agreed but added the caveat, "All [of the original findings] relate to pharmaceutical doses of ω3, not 'ω3 FA consumption,' which implies diet. Minimal effect of pharma doses when given with statins."	● FO: Overall still valid, but possible differences in different population (based on 1 large new trial) ● ALA: Possibly out of date (based on new trials)	**Quantitative:** FO: Change in statistical significance, Sig to SNS (B1) ALA: N/A **Qualitative:** FO: Opposing findings (A1) ALA: Opposing findings (A1)

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
HDL cholesterol				
19 RCTs (18 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 17. The studies "were heterogeneous, but mostly found small (0% to 6%), non-significant net increases in level of [HDL]." 18. "The effect of plant oils (ALA) on [HDL] was possibly weaker but similar to the effect of marine oils." 19. 17 fish oil studies: Summary net effect +1.6 (95% CI +0.8, +2.3) mg/dL[24] 20. 2 ALA studies: Range of net effects -1, +1 mg/dL[24] 21. No clear evidence of different effects in different populations 22. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of n-3 FA 23. "No clear effect across [or within 5] studies… based on duration of intervention or exposure." 24. No evidence on sustainment of effect.	From literature search: 14 RCTs (10 FO, 2 n-3 FA rich diet, 2 ALA) From experts: 3 RCTs (3 FO) 17. Most of the studies showed no significant effects on HDL. 18. 2 ALA studies (from literature search): no sig. effect 19. 10 fish oil studies (from literature search): FO groups had sig. higher HDL in 3 studies 3 fish oil studies (from experts): FO groups had sig. higher HDL in 2 studies 2 n-3 FA rich diet studies (from literature search): no sig. effect 20. 2 ALA studies (from literature search): no sig. effect 21. 3 fish oil studies: ● 1 study: Among those with normoglycemia or high-risk group (TG ≥150 mg/dL and HDL-C <40 mg/dL), no sig effect on HDL; Among those with impaired glucose metabolism, sig lower final HDL ● 2 studies: No different effects by the baseline LDL cholesterol or ethnicity	Four of five experts (one omitted the question) stated that the findings of the original report are almost or certainly still supported by the evidence; one stated that they are not. One stated that the previous findings are no longer supported, adding "There seems to be now a significant increase in HDL cholesterol." One omitted the question, but added, "Were the review to be updated an additional relevant question is whether the changes in HDL-C are dependent on the change in TG. Particularly important to split the studies on the basis of baseline TG…" One agreed the findings were still supported, adding the same caveats as he did above (LDL).	● FO: Overall still valid, but possible differences in different population (based on 1 large new trial and 2 medium size trials) ● ALA: Still valid	**Quantitative:** FO: Change in statistical significance, Sig to SNS (B1) ALA: N/A **Qualitative:** FO: Opposing findings (A1) ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
	22. 2 fish oil studies, **no clear evidence** of a **dose effect** 23-24. No new data were found.			
Triglycerides				
19 RCTs (18 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 25. "Most of [the] studies reported a net decrease in Tg of about 10% to 33%." "However, 1 of 2 studies of plant oils (ALA) found a net increase in Tg." 26. 17 fish oil studies: Summary net effect -27 (95% CI -33, -20) mg/dL; Higher baseline Tg and higher dose associated with larger effect..[24] 27. 3 ALA studies: Range of net effects -19, +23 mg/dL[24] 28. "The effect was… generally consistent among healthy subjects and patients with CVD, dyslipidemia, or at elevated risk of CVD." (No study of diabetic patients had sufficient number of subjects to be analyzed.) 29. "The effect was dose-dependent… [and] greater in studies with higher mean baseline	From literature search: 14 RCTs (11 FO, 2 n-3 FA rich diet, 1 ALA) From experts: 4 RCTs (4 FO) 10 of 18 studies found a sig. net decrease in TG, but other studies showed no sig. effects on TG. ● 11 fish oil studies (from literature search): sig. decrease in Tg in FO group in 6 studies. In 1 study, sig decrease when FO was given in diet but not without diet 4 fish oil studies (from experts): sig decrease in Tg in 2 studies 2 n-3 FA rich diet studies (from literature search): no sig. effect ● 1 ALA study (from literature search): No sig. effect ● 1 FO study: No difference with normoglycemia, impaired glucose metabolism, or high-risk group (TG ≥150 mg/dL and HDL-C <40 mg/dL) ● 2 FO studies: 1 study, sig. dose effect on TG for men, but not for women; 1 study, sig. dose effect on TG for	Five of the six experts stated that the findings of the original report are almost or certainly still supported by the evidence; one was undecided. One agreed the findings were still supported, adding, "all outcomes could be updated for ω3 in combination with statins."	● FO: Still valid ● ALA: Still valid	**Quantitative:** FO: No signal ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Tg." 30. "Limited data suggest the effect is not related to sex, age, weight, background diet, or lipid treatment." 31. "The effect of duration of intervention is unclear." 32. No evidence on sustainment of effect.	young groups, but not for older groups ● 1 FO study: No different effects by the baseline LDL cholesterol 31-32. No new data			
Lipoprotein (a) [Lp(a)]				
14 RCTs (13 FO, 1 ALA) (N≥5) 33. "No consistent effect on Lp(a) levels…. In approximately one-third of the studies the n-3 FA study arms had a net increase in Lp(a) level compared to control; in the remaining studies the net decrease in Lp(a) was generally small and non-significant." 34. No clear evidence of different effects in different populations 35. Evidence (in 2 studies directly, or across studies) of no different effects based on dose or based on exposure duration 36. Inadequate evidence regarding covariates, source or type of n-3 FA. 37. No evidence on sustainment of effect.	From our literature search: 6 RCTs (3FO, 3 n-3 FA rich diet) From experts: 1 RCT (1ALA) 33. 3 fish oil studies (from the literature search): ● 2 studies: No sig. effect on Lp(a) ● 1 study: Significantly different between two groups, DHA vs. control 3 n-3 FA rich diet (from the literature search): ● 2 studies: No sig. effect on Lp(a) 1 ALA study (from experts): No sig. effect on Lp(a) 34. No new data were found. 35. 1 fish oil study: No sig. dose effect 36. No new data were found. 37. No new data were found.	3 of 6 experts stated that the findings of the original report are almost or certainly still supported by the evidence; one was undecided, one omitted the question, and one recommended not updating this outcome.	● FO: Still valid ● ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Apolipoprotein A-1 (apo A-1)				
27 RCTs (27 FO, 2 ALA) (N≥20 [parallel design], N≥15 [crossover]) 38. The studies "generally found no effect or either a small increase or decrease in level with n-3 FA consumption." 39. "Limited evidence suggested that purified EPA may decrease apo A-1 levels while DHA has no effect, and that there is no difference in effect between fish oils and ALA." 40. No evidence of a dose effect or of different effects in different populations 41. One study reported no association in effect with sex, BMI, hypertension, and NIDDM. 42. Evidence (in 2 studies directly, or across studies) of no different effects based on exposure duration. 43. Three studies followed subjects after stopping the intervention. One found a persistent decrease in apo A-1 at 5 months, but the other two studies found no difference (from baseline) after 8 weeks and 6 months.	From our literature search: 6 RCTs (4 FO, 2 n-3 FA rich diet (1 of which had FO and ALA rich diets)) From experts: 3 RCTs (2 FO, 1 ALA) 38. 6 fish oil studies (from the literature search and experts): No sig. effect on apo-A1 1 ALA study (experts): A significant net decrease in change of apo-A1 39. 2 n-3 FA rich diet: No sig. effect on apo-A1. No effect of ALA 40. 2 n-3 FA rich diet: not significantly different between 2 groups (EPA/DHA vs. ALA rich diet) 41. 1 fish oil study: No sig. dose effect 42. No new data were found. 43. No new data were found.	3 of 6 experts stated that the findings of the original report are almost or certainly still supported by the evidence; one was undecided, one omitted the question, and one recommended not updating this outcome. One agreed that the findings were still supported, citing one study in which the "use of flaxseed increased apolipoprotein A-1 compared to placebo." One recommended not updating this outcome, adding, "However, were the variable retained the important question would be are the changes (or lack thereof) in apoA-1 similar to HDL…."	● FO: Still valid ● ALA: Possibly out of date (based on new trials)	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Apolipoprotein B (apo B)				
25 RCTs (24 FO, 2 ALA) (N≥20 [parallel design], N≥10 [crossover]) 44. "Little consistency in the effect of n-3 FA on apo B levels. About half… found a small net increase and half a small net decrease." 45. In contrasts to studies of other populations, the 4 studies of people with diabetes all found "small, non-significant net increases in apo B." 46. One study found a significantly greater rise in apo B level in younger, compared to older, participants. A different study found no difference related to intake of saturated fats. 47. Two of three studies found larger net decreases in apo B with higher doses of fish oil or dietary fish intake, but this effect was not confirmed across studies. There was no consistent evidence regarding differences among different sources of fish oils. 48. Inadequate evidence regarding effect of exposure duration. 49. In 3 studies, no clear	From our literature search: 9 RCTs (6FO, 3 EPA/DHA/ALA rich diet) From experts: 4 RCTs (3 FO, 1 ALA) 44. 7 fish oil studies (6 from the literature search and 1 from experts) ● 7 fish oil studies: No sig. effect on apo B 2 fish oil studies (from experts): Sig. decrease in change of apo B ● 1 ALA study (from experts): No sig. effect on apo B 3 n-3 FA/ALA rich diet: ● 2 studies: No sig. effect on apo B ● 1 study: ALA rich vs. control, ALA group had sig. lower apo B; n-3 FA rich vs. control, n-3 FA group had sig. higher apo B. 45. 1 fish oil study: No sig. effect on apo B (in Europeans and Indo-Asians) 46. No new data were found. 47. 1 fish oil study: No sig. dose effect 48. No new data were found. 49. No new data were found.	3 of 6 experts stated that the findings of the original report are almost or certainly still supported by the evidence; one was undecided, one omitted the question, and one recommended not updating this outcome. One recommended not updating this outcome, adding the same caveat as above (apo A-1) but for apo B and LDL.	● FO: Still valid ● ALA: Possibly out of date (based on new trials)	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
evidence of any sustainment of effect.				
Apolipoprotein B-100 (apo B-100)				
4 RCTs (4 FO, 0 ALA) (N≥5) 50. No consistent effect. 51. Insufficient data to evaluate differences across populations. 52. One study found no correlation between change in apo B-100 and sex, BMI, hypertension, or diabetes. 53. Inadequate evidence regarding different effects based on source or dose. 54. Possible evidence of no difference in effect based on exposure duration 55. No evidence on sustainment of effect.	No new data were found.	One expert stated that the findings of the original report are almost or certainly still supported by the evidence; two were undecided, one recommended not updating this outcome, and two omitted the question. Two of the experts omitted the question, but both added that this should be included as part of the apo B category.	● FO: Still valid ● ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal
LDL Apolipoprotein B (LDL apo B)				
6 RCTs (6 FO, 0 ALA) (N≥5) 56. Evidence suggests "large, [statistically] significant net increases in LDL apo B [of] 20-45 mg/dL." 57. Insufficient data to evaluate differences across populations. 58. One study found no correlation between change in LDL apo B and diet or body weight. 59. Inadequate evidence regarding different effects based on source or dose.	No new data were found.	Two of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; one was undecided, one recommended not updating this outcome, and two omitted the question. One omitted the question, but added that this outcome should certainly be dropped.	● FO: Still valid ● ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
60. Possible evidence of no difference in effect based on exposure duration 61. No evidence on sustainment of effect.				
Blood pressure				
Pre-existing SR in people without DM (36 RCTs, all FO) 6 RCTs (6 FO, 0 ALA) (DM, N≥15 [parallel design], N≥10 [crossover]) *SR in non-diabetics:* 62. Summary net change SBP -2.1 (-3.2, -1.0) mm Hg, DBP -1.6 (-2.2, -1.0) mm Hg. 63. SBP and DBP reductions were significantly larger in studies with mean ages ≥45 y, mean BP ≥140/90. No association with mean BMI, trial duration, or fish oil dose. Unable to assess sex. *RCTs of diabetics:* 64. "Generally small, non-significant effects on SBP and DBP", similar to meta-analysis of studies of non-diabetics 65. 1 study found no association between sex or Hb A1c and BP effect. No consistent differences across studies based on covariates. 66. Across studies no clear evidence of different effects based on dose, source, or duration of	15 RCTs (12FO, 1 ALA, 1 EPA/DHA, 1 ALA rich diet) 62-63. NA 64. 12 fish oil studies: ● 10 studies: No sig. effect on SBP and DBP ● 1 study: FO group, sig. decrease in SBP, DBP ● 1 study: FO group, sig. decrease in DBP, but not in SBP 1 ALA study (nondiabetics): ALA group, sig. decrease in SBP, DBP 1 EPA/DHA rich diet: No sig. effect on SBP, DBP 1 ALA rich diet (type 2 DM): Walnut-enriched vs. control diet, sig. increase in SBP, DBP 65. 1 study showed that the results were similar after adjusting for age, race, gender, and baseline DBP or SBP. 66. No new data were found. 67. No new data were found.	Four of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; one stated that they are not, and one was undecided.	● FO: Possibly out of date (mostly based on minority expert opinion) ● ALA: Probably out of date (based on trials)	**Quantitative:** FO (no DM): SBP: Change in statistical significance, Sig to NS (B1) DBP: Change in effect size of at least 50%, Sig -2 to Sig +0.4 mm Hg (B2) FO (w/DM): N/A ALA: N/A **Qualitative:** FO (no DM): SBP: Opposing findings (A1) DBP: Opposing findings (A1) FO (w/DM): No signal ALA: No signal (or A4, new trials where there were none)

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
exposure to FO. 67. No evidence on sustainment of effect.				
Hemoglobin A1c				
18 RCTs (18 FO, 0 ALA) (N≥10) 68. "n-3 FA had a very small, if any, effect on Hgb A1c levels compared to control." 69. Summary net effect 0.1% (95% CI -0.01, +0.2) ; Homogeneous[24] 70. No clear difference across studies based on sub-populations 71. 1 study found no correlation in effect with diet or body weight. Another study found no difference between men and women. 72. 2 studies found no difference in effect based on dose. Also no evidence of a dose effect across studies. 73. 2 studies found no overall difference in effect at different time points. 74. 1 study found that Hgb A1c remained unchanged 8 weeks after stopping supplementation.	5 RCTs (4FO, 1 ALA rich diet) 68-69. 4 fish oil studies: No sig. effect on Hemoglobin A1c ● ALA rich diet: No sig. effect on Hemoglobin A1c 70. 2 fish oil studies: No sig. difference across studies based on sub-populations 71-74. No new data were found.	Four of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; two were undecided.	● FO: Still valid ● ALA: Probably out of date (based on 1 new trial)	**Quantitative:** FO: No signal ALA: N/A **Qualitative:** FO: No signal ALA: No signal (or A4, new trial where there were none)

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Fasting glucose				
17 RCTs (18 FO, 0 ALA) (N≥25 [parallel design], N≥15 [crossover]) 75. "The effect of n-3 FA on [fasting glucose] was inconsistent across the studies." 76. Summary net effect 3.0 (95% CI -0.2, +6) mg/dL; Higher mean baseline fasting glucose and higher dose associated with larger net increases in fasting glucose.[24] 77. No clear difference across studies based on sub-populations 78. 3 studies found no correlations in effect with diet or body weight. 79. No evidence within or across studies suggesting differences based on source or dose (based on qualitative analysis). 80. 2 studies found no overall difference in effect at different time points. 81. 2 studies found that any changes in fasting glucose reverted to baseline after 8 or 12 weeks after stopping supplementation.	From update searcH: 12 RCTs (1 EPA, 1 FO vs EPA+DHA, 1 n-3 FA+ALA,1 Mediterranean diet, 3 n-3 FA, 1 fish oil, 1 EPA+DHA, 1 DHA, 1 walnut,) were identified. From experts: 2 RCTs (1 fish oil, fatty fish, lean fish diet vs. no fish control diet; 1 flaxseed vs. wheat germ) 75-76. One RCT that compared fish oil and corn oil reported sig. higher fasting glucose and lower glucose utilization in fish oil group compared with corn oil group. Another RCT sent from expert showed that subjects who consumed fish oil and fish diets had (median) decreases in fasting glucose, while control subjects did not (no statistical testing was done). All other RCTs (fish oil, n-3 rich diets or ALA) reported no sig. difference between groups, including the 1 ALA study sent from expert. 77-81. no new data were found.	Four of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; two stated that they are not.	• FO: Possibly out of date (based on minority expert opinion) • ALA: Probably out of date (based on new trials)	**Quantitative:** FO: Change in significance, NS to Sig (B1) ALA: N/A **Qualitative:** FO: No signal[a] ALA: No signal (or A4, new trials where there were none)

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Fasting insulin				
15 RCTs (18 FO, 0 ALA) (N≥5) 82. Baseline fasting insulin levels varied widely within and between studies, including differences between FO and placebo groups up to 60%. Across studies there was a very broad range of net percent changes in fasting insulin. 83. There was similar heterogeneity in effect in euglycemic and hyperglycemic populations. 84. 1 study of euglycemic participants found no interaction with weight loss (on a weight loss diet). No differences based on covariates could be discerned across studies. 85. No evidence suggests different effects based on dose or source. 86. 1 study reported no difference in effects at multiple time points to 6 months. 87. No evidence on sustainment of effect.	From update search: 10 RCTs (1 FO vs. EPA+DHA, 1 n-3 FA+ALA, 1 Mediterranean diet, 1 FO, 2 n-3 FA, 2 EPA+DHA, 1 DHA, 1 walnut) were identified. From experts: 2 RCTs (1 fish oil, fatty fish, lean fish diet vs. no fish control diet; 1 flaxseed vs. wheat germ) 82. Among the FO or EPA/DHA studies, no sig. effect was reported. Another RCT sent from expert showed that subjects who consumed fish oil and fish diets had (median) decreases in fasting insulin, while control subjects did not (no statistical testing was done). 83. One RCT comparing Mediterranean diet with low-fat diet found that sig. difference was found among diabetic participants, but not among non-diabetic participants. 84. One RCT that evaluated walnut intakes reported sig. higher fasting insulin in walnut group compared with placebo group, but no sig. diff in HOMA-IR. All other RCTs reported no sig. difference in fasting insulin or HOMA-IR between groups, including the 1 ALA study sent from expert. 85-87. No new data were found	One of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; two stated that they are not, one was undecided, one omitted the question, and one stated that they are supported but that the outcome should not be updated. One stated that the findings are not still supported, adding, "A recent review article points out that it might decrease insulin in subjects with non-alcoholic liver disease although the data need to be confirmed with randomized control trials."	• FO: Possibly out of date (based on minority expert opinion) • ALA: Probably out of date (based on new trials)	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal (or A4, new trials where there were none)

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
C-reactive protein (CRP)				
4 RCTs (4 FO, 0 ALA), 1 cross-sectional (Fish) (Any study) 88. No study found a significant effect of n-3 FA consumption on CRP level. 89. In one trial no difference in effect was seen among participants with elevated baseline CRP (>2 mg/L) 90. There was no evidence of a dose effect. 91. CRP levels were unchanged regardless of intervention duration up to 3 months. 92. No evidence on sustainment of effect.	From our literature search: 8 RCTs (1 herring, 1 DHA, 2 Mediterranean diet, 2 n-3 FA, 1 linseed oil, 1 ALA), 3 cross-sectional (2 n-3, 1 EPA+DHA, 1 non-fried fish, 1 ALA), 1 cohort (fish), 2 NRCS (n-6+fish oil, salmon) From experts: 2 RCTs (1 FO, 1 ALA) 88. (From search) No sig. effect in cohort study, 2 NRCS, and 7 RCTs; 1 RCT, sig. lower CRP in ALA vs. placebo; 1 XS study, lower CRP with increased nonfried fish intake, but not EPA+DHA intake; 1 XS study, lower CRP with increased n-3 FA intake, but not ALA; 1 XS study, sig. association among male exsmokers or female nonsmokers, but not male nonsmokers. (From experts) 1 RCT, nonsig ALA vs. placebo; 1 RCT, sig. reduction in CRP between pre- and post intervention for DHA group 89. No new data for effect modification by baseline CRP 90. No new data for dosage. 91. No new data for duration of intervention.	Two of the experts stated that the findings of the original report are almost or certainly still supported by the evidence (one stated that they are generally still true); two were undecided, and one recommended not updating this outcome.	• FO: Possibly out of date (based on new trials) • ALA: Probably out of date (based on new trials)	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal (or A4, new trials where there were none)

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
	92. 1 RCT: sig. decreased CRP in ALA vs. placebo at 1 & 2 y follow-up.			
Fibrinogen				
24 RCTs (22 FO, 3 ALA) (N≥15 [parallel design], N≥10 [crossover]) 93. No consistent effect on fibrinogen levels of n-3 FA consumption compared to control. 94. Subsets of studies evaluated healthy people, those with CVD or hypertension, dyslipidemia, and diabetes. No consistent difference in effect was seen across studies. But 2 studies found a large net decrease in fibrinogen with n-3 FA in those with hyperlipoproteinemia types IIb or IV, and a sig. net increase in those with insulin-dependent DM, respectively. 95. 5 studies found no association in effect with various factors including sex, baseline and change in weight, baseline blood pressure, changes in lipids or insulin, or cardiovascular, lipid or antithrombotic drug use, wine consumption, high- or low-fat diets.	93. 6 RCTs (1 FO, 1 herring, 2 n-3 FA, 1 ALA, 1 ALA vs. EPA/DHA vs. control) from update search and 1 RCT (flaxseed vs. wheat germ) from experts were identified. No study reported sig effect. 94-98. No new data were found.	Three of the experts were undecided; three recommended not updating this outcome.	• FO: Still valid • ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
96. There was no consistent dose effect or difference by n-3 source 97. There was no apparent difference in effect across 2 weeks to 2 years of consumption. 98. Two studies, which found no effect on fibrinogen, also found no further change 4 weeks or 6 months after stopping the intervention.				
Factor VII				
19 RCTs (17 FO, 3 ALA) (N≥15 [parallel design], N≥10 [crossover]) 99. There was no consistency in effect across studies. Any net changes were small (<7%). 100. Two of three studies of people with diabetes found a statistically significant net increase in factor VII. No consistent effects were found in different populations. 101. Possible associations between effect size and covariates were analyzed by 3 studies, but there were no consistent findings. 102. Across studies, there was no evidence of a dose effect. Within studies there was no	99. 3 RCTs (2 n-3 FA, 1 control vs. ALA vs. EPA/DHA of a variety of treatment combinations were identified. No sig effect of n-3 FA on factor VII was reported. 100-104. No new data were found.	One of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; two were undecided and three recommended not updating this outcome.	• FO: Still valid • ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
evidence of different effects with different n-3 FA sources. 103. Across studies, duration of intervention had no effect. 104. In one study, there continued to be no effect on factor VII 1 month after stopping the intervention.				
Factor VIII				
5 RCTs (4 FO, 1 ALA) (N≥5) 105. There was no consistency in effect across studies. 106. The single stuffy of insulin dependent diabetics found a larger, though non-significant net increase of factor VIII than studies of the general population. 107. One study found no association between effect size and sex or Hgb A1c in insulin dependent diabetics who were also taking aspirin. 108. One study found no fish oil dose effect. The evidence across studies was unclear regarding differential effects based on source or type of n-3 FA.	105-110. No new data were found.	One of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; two were undecided and three recommended not updating this outcome.	• FO: Still valid • ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
109. Three studies found no consistent effect across a range of intervention durations from 3 weeks to 12 months. 110. In one study there was no change in factor VIII 1 and 2 months after stopping the intervention.				
von Willebrand Factor (vWF)				
9 RCTs (8 FO, 1 ALA) (N≥5) 111. Most studies found a net decrease in vWF (up to 13%), though only one study found a statistically significant difference. 112. No clear pattern in effect was seen across populations. 113. The studies do not allow conclusions about the effect of covariates. 114. One study each found no dose effect and no difference between fish oil type. There was no consistent effect based on dose or type across studies. 115. Two studies found no consistent effect across a range of intervention durations from 3 weeks to 12 months.	111. No sig effect was found is any of the 3 RCTs identified. In one RCT, stratified analysis by presence or absence of diet intervention did not change the results. 112-116. No new data were found.	Three of the experts were undecided and three recommended not updating this outcome.	• FO: Still valid • ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
116. In one study there was no change in factor VIII 1 and 2 months after stopping the intervention.				
Platelet aggregation				
11 RCTs (8 FO, 5 ALA) (N≥15 [parallel design], N≥10 [crossover]) 117. Large heterogeneity of methods to measure platelet aggregation. 118. "Heterogeneous effects … depending on aggregating agent, dose of the agent, and measurement metric used. [In] most studies either no effect on platelet aggregation with n-3 FA or no difference in effect …." 119. No evidence of differential effects in different populations, by health status, weight, age, or sex. or covariates smoking and alcohol consumption, within and across studies. 120. No study compared different doses of n-3 FA. No dose effect was seen across studies. Two studies disagreed whether platelet aggregation differed with fish oil or ALA. One concluded that pure	117. From update search: 2 RCTs (1 FO, 1 ALA) and 1 non-randomized comparative study (FO) reported a variety of platelet aggregation measurements. From experts: 1 RCT (1 g n-3 with aspirin and clopidogrel vs. placebo with aspirin and clopidogrel) platelet aggregation to ADP was sig. reduced, but platelet aggregation to arachidonic acid was not sig. different. 118. One RCT and one comparative study found no sig diff among treatment groups in one measure, but sig diff in another measure. 119. In one study, collagen induced platelet aggregation was sig reduced in an older group (age 45-69) but not in younger group (age 18-29). There were no sig diff between treatment groups in thrombin aggregation in both age groups. 120. No new data on dosage were found. 121. No new data on the effect of time consuming n-3 FA were found. 122. No new data were found.	Three of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; two were undecided and one omitted the question. One omitted the question, but added that "combination data is important to add here" and that "safety is clear in combination with other agents."	● FO: Still valid ● ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
DHA is less potent at reducing aggregation than fish oil or dietary fish at moderate doses. 121. No clear effect of time consuming n-3 FA was seen in 3 studies. 122. One study found that one measure of platelet aggregation did not return to baseline during a 12 week follow-up after stopping the trial; though other tests did.				
Coronary arteriography				
12 RCTs (12 FO, 0 ALA) (N≥5) 123. "Overall, although there is heterogeneity among studies, there is a trend toward a net reduction of coronary artery restenosis with fish oil supplementation." Random effects model RR = 0.87 (95% CI 0.73, 1.05). 124. All studies included patients undergoing PTCA. The studies that performed multivariate analyses including diabetes, lipid and cardiovascular variables generally found no association between these covariates and restenosis rates. Two	No new data were found.	Two of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; one stated that they do not, two were undecided, and one omitted the question.	• FO: Possibly out of date (based on minority expert opinion) • ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
studies found no difference between men and women. 125. The heterogeneity of the studies was not explained by either dose or treatment duration. 126. No evidence on sustainment of effect.				
Carotid intima media thickness (IMT)				
1 RCT (FO), 1 longitudinal cohort (ALA), 2 cross-sectional (1 dietary ALA, 1 fishing vs farming village) (Any study) 127. The only RCT of fish oil found no significant net effect on carotid IMT. The longitudinal study of ALA was consistent with the RCT. The cross sectional studies both found that higher n-3 FA intake was associated with thinner IMT. 128. Insufficient evidence to evaluate subpopulations, covariates, dose effect, source effect, exposure duration, or sustainment of effect.	127. 2 RCTs (1 ALA, 1 EPC) found no sig effect on IMT. 2 ALA cross-sectional studies: 1 sig and 1 NS 1 non-fried fish cross-sectional study: no sig effect 2 n-3 FA cross-sectional studies: sig lower IMT with increased n-3 FA intakes. 1 cross-sectional study found sig lower IMT with increased EPA, DPA, or DHA intakes. 128. No new data on subpopulations, covariates, dose effect, exposure duration, or sustainment of effect were found.	Two of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; three were undecided and one omitted the question.	• FO: Still valid • ALA: Probably out of date (based on 1 new trial)	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal (or A4, new trial where there were none)

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Exercise tolerance testing				
3 RCTs (3 FO, 0 ALA), 3 longitudinal cohorts (3 FO, 0 ALA) (Any study) 129. Studies suggest that fish oil consumption may benefit exercise capacity among patients with coronary artery disease, although the effect may be small. 130. Insufficient evidence to evaluate subpopulations, covariates, dose effect, source effect, exposure duration, or sustainment of effect.	129. No new data were found. 130. No new data were found.	Three of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; one was undecided, one recommended not updating this outcome, and one omitted the question.	• FO: Still valid • ALA: Probably out of date (based on 1 new trial)	**Quantitative:** FO: N/A ALA: N/A **Qualitative:** FO: No signal ALA: No signal

Table B3. Updating effects of omega-3 fatty acids on cardiovascular disease risk factors (continued)

Conclusions in 2004 Report	Updated Literature Search and Articles From Experts	Expert Opinion	Conclusions from EPC	Ottawa Update Signals
Heart rate variability				
2 RCTs (2 FO, 0 ALA), 1 cross-sectional (FO) (Any study) 131. The 3 studies, all by the same set of investigators, found that there was no significant effect of fish oil on heart rate variability in healthy volunteers, but may increase (improve) heart rate variability in survivors of myocardial infarction. 132. There is possible evidence of a dose effect.	From our literature search: 2 RCTs (n-3 FA) and 1 cohort study (dark fish, n-3 FA) From experts: 3 RCTs (n-3 FA) 131. The 3 studies from the literature search did not find sig effect on heart rate variability. The 3 studies from the experts all found significant improvements in heart rate variability with fish oil. 132. 1 study (from experts) found a dose effect.	Two of the experts stated that the findings of the original report are almost or certainly still supported by the evidence; two were undecided, one recommended not updating this outcome, and one omitted the question. One agreed, adding that there is "more data in support of improved HRV."	● FO: Probably out of date (based on minority expert opinion, 1 new trial from literature search, and 3 new trials from experts that disagreed with report) ● ALA: Still valid	**Quantitative:** FO: N/A ALA: N/A **Qualitative[b]:** FO: No signal ALA: No signal
Additional risk factors suggested: ● Suppression of arrhythmias ● Specific cardiac arrhythmias (e.g., atrial vs. ventricular) ● Lipoprotein-associated phospholipase A2 (Lp-PLA2).				

[a]Discrepancy between "B1" and "No Signal" is due to one large trial that reported no significant effect, but from reported data changed the meta-analysis from nonsignificant to significant.

[b]Note that the trials found by the experts were not included in the Ottawa qualitative analysis.

ALA = alpha linolenic acid; BMI = body mass index; BP = blood pressure; CRP = C-reactive protein; CVD = cardiovascular disease; DBP = diastolic blood pressure; DHA = docosahexaenoic acid; DM = diabetes mellitus; EPA = eicosapentaenoic acid; FA = fatty acid; FO = fish oil; HDL = high-density lipoprotein; Hgb = hemoglobin; LDL = low-density lipoprotein; LP = lipoprotein; PTCA = percutaneous transluminal coronary angiography; RCT = randomized controlled trial; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; vWF = von Willebrand Factor

Table B4. Fish oil matrix, "RAND" versus "Ottawa" methods

			"RAND"			
			Definitely Out of Date	**Probably Out of Date**	**Possibly Out of Date**	**Still Valid**
"Ottawa"	**Quantitative Analysis**	**B1**			Total cholesterol Fasting glucose SBP (no DM)	LDL (with caveat) [1] HDL (with caveat) [1]
		B2			DBP (no DM)	
	Qualitative Analysis	**A1**				
		A2				
		A3				
		A4				
		A5				
		A6				
		A7				
	No Signal			HRV	SBP (w/DM) DBP (w/DM) Fasting insulin CRP Coronary arteriography	Tg Lp (a) Apo A-1 Apo B Apo B-100 LDL Apo-B Hb A1c Fibrinogen Factor VII Factor VIII vWF Platelet aggregation Carotid IMT ETT

Apo=apolipoprotein; CRP=C reactive protein; DBP=diastolic blood pressure; DM=diabetes mellitus (indicating the eligibility criterion); ETT=exercise tolerance testing; Hb A1c=hemoglobin A1c; HDL=high density lipoprotein cholesterol; HRV=heart rate variability; IMT=intima media thickness; LDL=low density lipoprotein cholesterol; Lp (a) =lipoprotein (a); SBP=systolic blood pressure; TG=triglycerides; vWF=von Willebrand factor.
Gray shaded boxes indicate discordance between RAND and Ottawa methods.
[1] One very large trial had discordant results with almost all other trials. Our consensus was that this one outlier trial did not invalidate the original overall conclusions.

Table B5. ALA matrix, "RAND" versus "Ottawa" methods

			"RAND"			
			Definitely Out of Date	**Probably Out of Date**	**Possibly Out of Date**	**Still Valid**
"Ottawa"	**Quantitative Analysis**	**B1**				
		B2				
	Qualitative Analysis	**A1**			Total cholesterol LDL	
		A2				
		A3				
		A4		*		
		A5				
		A6				
		A7				
	No Signal			SBP* DBP* Hb A1c* Fasting glucose* Fasting insulin* CRP* Carotid IMT*	Apo A-1 Apo B	HDL TG Lp (a) Apo B-100 LDL Apo-B Fibrinogen Factor VII Factor VIII vWF Platelet aggregation Coronary arteriography ETT HRV

Apo = apolipoprotein; CRP = C reactive protein; DBP = diastolic blood pressure; DM = diabetes mellitus (indicating the eligibility criterion); ETT = exercise tolerance testing; Hb A1c = hemoglobin A1c; HDL = high density lipoprotein cholesterol; HRV = heart rate variability; IMT = intima media thickness; LDL = low-density lipoprotein cholesterol; Lp (a) = lipoprotein (a); SBP = systolic blood pressure; TG = triglycerides; vWF = von Willebrand factor.
Gray shaded boxes indicate discordance between RAND and Ottawa methods.
* Original review had no studies. Updated search found small new trials found for each. Thus, these could be interpreted as having an A4 signal.

Of 6 experts, votes to not update outcomes:

Lipoprotein (a)	1
Apolipoprotein A-1	1
Apolipoprotein B	1
Apolipoprotein B-100	2
LDL Apolipoprotein B	1
Fasting insulin	1
C reactive protein	1
Fibrinogen	3
Factor VII	3
Factor VIII	3
Exercise tolerance testing	1
Heart rate variability	1

From 6 experts, additional cardiovascular risk factors or intermediate markers suggested for updated report:
Cardiac arrhythmias (both atrial and ventricular)
Lipoprotein-associated phospholipase A2 (Lp-PLA2).

Appendix C. Evidence Tables

Cognitive Function

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Key Question 1 – Cognitive Function				**2005 Report Conclusion –** -1 study (n=818, all men), found weak evidence of positive effect -Fish consumption weakly associated with reduced risk of cognitive impairment; no association with cognitive decline -Omega-3 FA consumption not associated with cognitive impairment or decline
Atherosclerosis Risk in Communities (ARIC) Beydoun, 2007[28]	N: 2,251 subjects in Minnesota Inclusion: Age 50+ Exclusion: None specified	Design: Prospective cohort study Intervention: None; primary independent variable was plasma fatty acid concentration of n-3 HUFAs (DHA + EPA) at baseline, reported as two biomarkers – phospholipids fraction and cholesteryl ester Other independent variables: Broad set of nutritional, demographic, and clinical measures Duration: 6 years change in cognition; cognitive testing was done at 3 and 9 years after baseline plasma sampling	Condition: Cognitive function Outcomes: Odds ratio of a composite measure of global cognitive decline across three tests (delayed word recall, digit symbol substitution, and word fluency), called the Reliable Change Index (RCI), set at a threshold value of RCI to indicate decline.	The adjusted OR was not significant for a one SD change in cholesteryl ester or plasma phospholipid fractions for total n-3 PUFAs, EPA, or DHA, and global cognitive decline. Subgroup analysis found that subjects with higher plasma DHA+EPA had a significantly lower OR for decline in verbal fluency in both plasma biomarkers. DHA+EPA were significantly more protective in subjects with hypertension, dyslipidemia, and low depression scores. Conclusion: Plasma fatty acid concentrations of n-3 PUFAs are protective against cognitive decline for some groups.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Atherosclerosis Risk in Communities (ARIC) Beydoun, 2007[28] (cont.)				Comparison to 2005 report: Meets criterion A4, important changes in effectiveness. Some evidence of a positive effect, new information about interactions
Atherosclerosis Risk in Communities (ARIC)[a] Beydoun, 2008[29]	N: 7,814 subjects in 4 U.S. communities Inclusion: Age 50+ Exclusion: None specified	Design: Prospective cohort study Intervention: None; primary independent variable was n-3 PUFA and HUFA intake as % of total energy intake, measured by Willett dietary FFQ at baseline and at 6 years (n=7,814). Plasma FA data were also reported for a subset of subjects (n=2,251), using the same data from Beydoun 2007 Other independent variables: Broad set of nutritional, demographic, and clinical measures Duration: 6 years change in cognition; cognitive testing was done at 3 and 9 years after baseline plasma sampling	Condition: Cognitive function Outcomes: OR as defined in Beydoun 2007 for global cognitive decline, and additionally for each individual cognitive test	Increased dietary intake of long-chain n-3 FA and balancing n-3:n-6 FA ratio decreased the risk of cognitive decline in verbal fluency, but not the other 2 cognitive tests or for global cognitive function. This finding also held for plasma biomarkers of cholesteryl ester and phospholipid fractions. Significant effects were more pronounced among hypertensive subjects, dietary intake and plasma variables. Conclusion: Dietary intake of n-3 FAs are protective against cognitive decline in verbal fluency for hypertensive subjects. Comparison to 2005 report: Meets criterion A4, important changes in effectiveness, and A6, clinically important caveat. Some evidence of a positive effect, new information about interactions.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Older People And n-3 Long-chain poly-unsaturated fatty acids (OPAL) Dangour, 2010[30]	N: 867 subjects from 20 general practices in the U.K.; 55% men Inclusion: Healthy, age 70–79 Exclusion: Current diagnosis of dementia or diabetes, recent bereavement, terminal illness, current daily use of fish oil supplements, Mini-Mental State Exam (MMSE) score <24	Design: Randomized, double-blind, placebo-controlled study Intervention: Dietary supplement of 2 x 650-mg pills, treatment (200 mg EPA and 500 mg DHA) or placebo group (olive oil - n-9 fatty acids). Other independent variables: Sociodemographic and medical factors, frequency and type of fish consumption, GHQ-30 score Duration: 24 months of treatment	Condition: Cognitive function in healthy subjects Outcomes: Mean score on a memory test from the California Verbal Learning Test (CVLT); secondary outcomes were mean scores of other tests of memory (story recall, spatial memory), processing speed, reaction time, and executive function	After 24 months of treatment, there was no difference in primary or secondary cognitive function measures between treatment and control groups. Conclusion: Fish oil supplementation does not affect cognitive function in healthy older people. Comparison to 2005 report: Does not meet criteria for change. Additional evidence strengthens prior conclusions of no effect.
Folic Acid and Carotid Intima-media Thickness (FACIT) trial Dullemeijer, 2007[31]	N: 404, age 50–70, 71% male subjects from a population study in the Netherlands Inclusion: Subjects were drawn from the placebo arm of a randomized study of folic acid supplementation Exclusion: No notable exclusions (e.g., inadequate blood sample, refusal to participate)	Design: Prospective cohort study Intervention: None; primary independent variable was plasma cholesteryl esters of n-3 PUFAs (sum of EPA + DPA + DHA levels) Other independent variables: Broad range of dietary, demographic, clinical, and genotype variables. Duration: 3 years	Condition: Cognitive function Outcomes: Performance on 5 cognitive tests that measured sensorimotor speed, complex speed, memory, information processing speed, and word fluency	Longitudinal analysis over 3 years found increased concentration of plasma n-3 PUFAs was associated with a small but significantly better performance on sensorimotor speed and complex speed tests, but not significantly associated with the other 3 cognitive tests. Cross-sectional analysis found no significant association. Conclusion: The study provides weak evidence of a small but positive link between plasma n-3 PUFA concentration and cognitive function. Comparison to 2005 report: Does not meet criteria for change. Additional evidence strengthens prior conclusions of weak effect.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Etude du Vieillissement Arteriel (EVA) cohort Heude, 2003[32]	N: 246, age 63–74, 41% male, from Nantes, France Inclusion: None specified Exclusion: None specified	Design: Prospective cohort study Intervention: None; primary independent variable was plasma erythrocyte n-3 PUFA concentration Other independent variables: Age, sex, education level, initial MMSE score Duration: 4 years	Condition: Cognitive decline Outcomes: Risk of a small cognitive decline of 2+ points on MMSE test; adjusted odds ratio of a moderate (1 SD) difference in cognitive decline	Subjects with small cognitive decline (2+ point MMSE) in 4 years had significantly lower plasma concentrations of total n-3 PUFAs, DHA, EPA, n-3:n-6 ratio, and DHA:AA ratio. The OR for a moderate cognitive decline (1-SD difference) was significantly lower for subjects with higher plasma levels of all of the above, except EPA. Conclusion: The study finds evidence that plasma n-3 PUFA levels are correlated with cognitive decline. Comparison to 2005 report: Meets criterion A4, important changes in effectiveness. Evidence of a positive effect.
Johnson, 2008[33]	N: 49 women from the general U.S. population, age 60–80 Inclusion: Healthy, non-smoking Exclusion: Taking mineral oil or medications that interfere with fat-soluble vitamin absorption, use of steroids or NSAIDs or antihistamines, recent nutrient or carotenoid supplement use, selected medical conditions	Design: Randomized, controlled study Intervention: Placebo (n=10), DHA (n=14), lutein (n=11), or DHA+lutein (n=14) treatment, all subjects also took BoostPlus nutritional energy drink Other independent variables: FFQ at baseline, 2 months, and 4 months, including DHA and lutein intake Duration: 4 months	Condition: Cognition (and eye health) Outcomes: Mean and SD of score on measures from nine different validated cognitive tests of memory, processing speed, attention, and mood	Only the verbal fluency test delayed recall showed significant improvement in performance for the DHA and DHA+lutein group, as compared to placebo. The MIR apartment test's delayed recall measure also showed significant improvement in the DHA+lutein group only. Conclusion: There is positive, but very weak evidence of a benefit of DHA supplementation on cognitive function. Comparison to 2005 report: Does not meet criteria for change.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Chicago Health and Aging Project Morris, 2005[34]	N: 3,718 subjects, aged 65+ in a Chicago, IL community Inclusion: None specified Exclusion: Invalid FFQ	Design: Prospective cohort study Intervention: None; primary independent variable was dietary intake of fish (not specific to fatty fish) assessed once by FFQ (median of 1.2 years from baseline evaluation); omega-3 FA levels derived from FFQ report Other independent variables: Broad set of dietary, demographic, cognitive, physical, lifestyle, medical, and psychological variables Duration: 6 years	Condition: Cognitive decline Outcomes: Rate of cognitive decline in a global cognitive score derived from 4 standardized tests	In an expanded adjustment model (but not in a basic model), rate of cognitive decline was significantly slower in subjects that consumed fish one or two times a week, compared to those that consumed fish zero times a week. A model adjusting for various dietary intakes did not find consistent evidence of a trend between quartile of fish intake and rate of change in cognitive score. Conclusion: The study found weak evidence of a positive association between fish consumption and slower cognitive decline. Comparison to 2005 report: Does not meet criteria for change. Additional evidence strengthens prior conclusions of weak effect.
Three-city (3C) study Samieri, 2010[35]	N: 1,228 community dwellers in Bordeaux, Dijon, and Montpelier, France, aged 65+, mean age 74, 39% male Inclusion: Noninstitutionalized Exclusion: Dementia at baseline, incomplete MMSE at followup	Design: Prospective cohort study Intervention: None; primary independent variable was plasma fatty acid proportions of EPA and DHA Other independent variables: Socio-demographic information, major medical risk factors, medical use, ApoE-e4 allele carrier status Duration: Followup at 2, 4, and 7 years after baseline exam	Condition: Cognitive decline Outcomes: Average annual change in mean and SD of score on MMSE, Isaacs Set Test (IST), Benton Visual Retention Test (BVRT), and Trail-Making Test A and B (TMT-A and –B)	ApoE-e4 carriers had significantly higher average annual decline on MMSE than noncarriers, although the amount of change was small (-0.21 vs. -0.12 for mean scores 27.35 and 27.54). In adjusted models, neither plasma DHA nor plasma EPA proportion were significantly associated with change in any of the four cognitive scores over time. However, ApoE-e4 carrier status increased the predicted mean BVRT score decline over time, with the lowest plasma DHA groups seeing the largest decline. The same conclusion was found for plasma

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Three-city (3C) study Samieri, 2010[35] (cont.)				EPA, but high depressive symptoms had an additive effect on cognitive decline for low-EPA groups. Conclusion: Plasma EPA and DHA are associated with cognitive decline over time, and ApoE-e4 carrier status and depressive symptoms (for DHA) strengthen this relationship. Comparison to 2005 report: Meets criterion A4, important change in effectiveness, and criterion A6, clinically important caveat. Evidence of a positive effect, new information about modulation by ApoE-e4 status.
Van de Rest, 2008[36]	N: 302 , mean age 70, 55% male subjects in the Netherlands Inclusion: Cognitively healthy (MMSE >21), 65+ years old Exclusion: Depression, MMSE score <21, current or recent fish oil supplement use, intake of more than 800 mg EPA-DHA from fish per day, use of antidepressant or dementia medications; use of more than 4 glasses of alcohol per day	Design: Randomized, double-blind, placebo- controlled study Intervention: Fish oil supplement in low and high doses (400 or 1,800 mg EPA-DHA), or placebo (high-oleic sunflower oil) Other independent variables: Medical history, drug use, alcohol consumption, smoking habits, educational, and marital status. Duration: 26 weeks	Condition: Cognitive function Outcomes: Score and changes in z scores of cognitive tests for sensorimotor speed, executive function, memory, and attention	There was no difference in scores on any of the cognitive tests at baseline, 13, and 26 weeks of treatment for the low-dose, high-dose, or placebo groups. Changes in z scores were not significant either. Conclusion: The study found that supplementation with EPA-DHA did not change cognitive function in healthy subjects. Comparison to 2005 report: Does not meet criteria for change. Additional evidence strengthens prior conclusions of no effect.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Veterans Administration Normative Aging Study (NAS) Van de Rest, 2009[37]	N: 313 male U.S. veterans aged 21–81 (mean age 42) Inclusion: None specified Exclusion: Fish oil or cod liver use	Design: Prospective cohort study Intervention: None; primary independent variable was Willett FFQ including fatty fish intake (tuna and dark-meat fish including bluefish, mackerel, salmon, sardines, swordfish) and n-3 PUFA derived from fatty fish intake. Diet assessed at baseline only. Other independent variables: Education, medical history Duration: 6 years	Condition: Cognitive function Outcomes: 6-year cognitive change in mean and SD scores for cognitive tests including memory, language, speed, and visuospatial ability	Cognitive function did not differ across quartiles of fish or n-3 PUFA intake at 6-year follow-up. Conclusion: Long-term cognitive function is not associated with n-3 PUFA or fatty fish intake. Comparison to 2005 report: Does not meet criteria for change. Additional evidence strengthens prior conclusions of no effect.
Zutphen Elderly Study[b] Van Gelder, 2007[38]	N: 210 men, age 70–89, in the Netherlands Inclusion: Healthy subjects Exclusion: Myocardial infarction, stroke, diabetes, cancer at baseline	Design: Prospective cohort study Intervention: None; primary independent variable was the cross-check dietary history assessment at baseline only; analysis was done for total fish consumption and EPA+DHA intake Other independent variables: Demographic, lifestyle, medical information, alcohol/tobacco use, depression scale Duration: 5 years	Condition: Cognitive function Outcomes: 5-year decline in MMSE score	Men who consumed no fish on a daily basis had significant MMSE decline over 5 years, whereas those who consumed 0-20 or >20 g/day did not have significant cognitive decline. Men in the lowest tertile of EPA+DHA intake also had significant decline in cognitive function, whereas the 2nd and 3rd tertiles did not. Conclusion: Low fish consumption and low EPA+DHA intake levels are significantly associated with cognitive decline over 5 years in healthy men. Comparison to 2005 report: Meets criterion A4, important changes in effectiveness. Evidence of positive effect.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Whalley, 2008[39]	N: 113 subjects in Scotland, aged 63-66 years old Inclusion: Independent living, community dwelling Exclusion: Dementia	Design: Prospective cohort Intervention: None; primary independent variable was plasma fatty acid content of erythrocyte membranes (total n-3 PUFA, DHA, EPA, n-6:n-3 ratio) measured at baseline Other independent variables: APOE genotype Duration: 2 and 4-year	Condition: Cognitive function Outcomes: Cognitive test scores at age 64, 66, and 68 for the: MMSE, Raven's Standard Progressive Matrices (RPM) of non-verbal reasoning, Rey's Auditory Verbal Learning Test (AVLT), Uses of Common Objects, Block Design and Digital Symbol subtests of the Weschler Adult Intelligence scale	Total n-3 PUFA and DHA erythrocyte levels are positively associated with overall cognitive function over time. When adjusted for ApoE-e4 carrier status, the DHA relationship remains significant only for non-carriers. Conclusion: n-3 PUFA and DHA levels are associated with cognitive function over time, but the trend is more consistent for non-carriers of the ApoE-e4 allele. Comparison to 2005 report: Meets criterion A4, important changes in effectiveness, and A6, clinically important caveat. Evidence of a positive effect, new information about ApoE-e4 status
Yurko-Mauro, 2010[40]	N: 485 subjects aged 55+ years at 19 U.S. sites Inclusion: Subjective memory compliant, met criteria for the DSM IV definition of age-related cognitive decline Exclusion: MMSE score <26, high memory recall scores, use of DHA or omega-3 supplements, medications for Alzheimers Disease, major antipsychotics, or anti-depressants, major medical conditions, alcohol/drug abuse	Design: Randomized, double-blind, placebo-controlled trial Intervention: 900 mg DHA per day vs. placebo (corn/soil oil capsules) Other independent variables: FFQ including DHA and long-chain PUFA intake Duration: 12 and 24-week follow-up	Condition: Cognitive function Outcomes: Primary outcome was change in Cambridge Neuropsychological Test Automated Battery (CANTAB) Paired Associated Learning (PAL) test. Numerous other secondary tests included other CANTAB tests, MMSE, and self-assessed memory.	The DHA group improved significantly on scores for CANTAB PAL, verbal recognition memory (immediate and delayed recall), and Stockings of Cambridge problem-solving after 24 weeks of treatment. No significant change was seen in 4 other cognitive test scores. Conclusion: DHA supplementation improves episodic memory and learning in healthy, older adults with mild memory complaints. Comparison to 2005 report: Meets criterion A4, important changes in effectiveness. Evidence of positive effect.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Key Question 2 – Incidence of dementia/ Alzheimer's disease				**2005 Report Conclusion –** -3 studies (n=5,386, 1,122, and 815), consistent evidence of positive effect -Fish intake associated with reduced risk of Alzheimer's dementia in 1 study, but not significant in other 2 studies -In 1 study, total omega-3 FA and DHA intake associated with reduced Alzheimer incidence, but not ALA or EPA
Three-City (3C) Study Barberger-Gateau, 2007[41]	N: 8,085 community dwelling adults in Bordeaux, Dijon, and Montepelier France, age 65+ Inclusion: None specified Exclusion: Dementia at baseline	Design: Prospective cohort study Intervention: No intervention; dietary assessment by FFQ at baseline to ascertain total weekly intake of fish and various fats, including omega-3 rich oils Other independent variables: Sociodemographic information, vascular risk factors, medical history, BMI Duration: 4 years	Condition: Dementia, including AD Outcomes: Incidence and hazard ratio (HR) of dementia (n=281), including AD (n=183)	Regular users of omega-3 rich oils were less likely to develop dementia or AD, and fish intake was also significantly correlated, although the trend was not consistent across increasing fish intake levels. For APOE e4 allele non-carriers, consumption of fish 2–3 times/week reduced the risk of dementia or AD compared to 0–1 times/week, but fish intake 4+ times/week was not significant. The HR for dementia based on regular intake of omega-3 rich oil was lower (p=0.05) in 1 adjustment model, but not in 2 other models; this HR for AD was not significant. Conclusion: The study found some evidence that the incidence of dementia was higher for low fish intake, the incidence of AD was lower for high fish intake, and risk of both conditions was lowers with regular use of omega-3 rich oils. Trends are not consistent with

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Three-City (3C) Study Barberger-Gateau, 2007[41] (cont.)				increasing fish intake levels, however. Comparison to 2005 report: No criteria for change met. Some positive effect found, consistent with prior conclusion
Rotterdam Study[c] Devore, 2009[42]	N: 5,395 subjects in the Netherlands Inclusion: Free of dementia at baseline Exclusion: Questionable cognitive status, nursing home residence, invalid/incomplete dietary interview responses	Design: Prospective cohort study Intervention: None. Main independent variable was dietary intake at baseline only, using a home-based checklist and dietician-administered FFQ that included total and fatty fish intake; data converted to n3-PUFAs (ALA, DHA, EPA). Other independent variables: Numerous medical/other variables Study was part of a broad population-based study of disease Duration: 10-year average followup	Condition: Dementia and AD Outcomes: Adjusted hazard ratios of incident dementia and AD	Increasing intake of total fish, fatty fish, long-chain omega-3 FA, EPA, and DHA was not associated with a significant HR for developing dementia or AD. Conclusion: The study provides consistent evidence of no association between the incidence of dementia or AD and intake of fish, fatty fish, long-chain omega-3 FA, EPA, or DHA. Comparison to 2005 report: Meets criterion A7, opposing findings from a non-pivotal trial. Conflicts with original findings of a positive effect.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Cardiovascular Health Cognition Study (CHCS)[d] Huang, 2005[43]	N: 2,233 subjects in 4 U.S. communities enrolled from Medicare eligibility lists Inclusion: Age 65+ Exclusion: Prevalent dementia or mild cognitive impairment at baseline; invalid FFQ responses	Design: Prospective cohort study Intervention: None; primary independent variable was dietary intake of fish (tuna, fried fish, fish sandwich, or other fish, baked or broiled) assessed once by FFQ at baseline Other independent variables: Age, education, race, gender, BMI, income Duration: Average 5.4 year followup to incidence, max 8.4 year followup	Condition: Dementia and AD Outcomes: Adjusted hazard ratios of incident dementia and AD	Increased consumption of tuna or other fish, but not of fried fish, was associated with a decreased HR of dementia and AD. When stratified by APOE e4 status, noncarriers had a reduced HR of dementia with higher intake of tuna or other fish, although carriers had no significant trends. Conclusion: Intake of some types of fish may reduce risk of developing dementia, but only in APOE e4 noncarriers. Comparison to 2005 report: Meets criterion A6, clinically important caveat. Consistent with positive effect findings, but adds new information about ApoE-e4.
Canadian Study of Health and Aging (CSHA) Kroger, 2009[44]	N: 663 subjects in Canada, 65+ years old Inclusion: None specified. Exclusion: Dementia at baseline	Design: Prospective cohort study Intervention: None; primary independent variable was plasma erythrocyte membrane level of total n-3 PUFA, DHA, EPA, and mercury Other independent variables: ApoE-e4 carrier status Duration: 4.9-year median follow-up	Condition: Dementia, including AD Outcomes: Adjusted hazard ratios of incident dementia	There was no significant relationship between continuous levels or quartiles of total n-3 PUFA, DHA, EPA plasma levels and incidence of dementia or AD. Adjustment for ApoE-e4 status and mercury levels did not change this result. Conclusion: Plasma n-3 PUFA, DHA, and EPA levels are not associated with incidence of dementia or AD. Comparison to 2005 report: Meets criterion A7, opposing findings from a nonpivotal trial; conflicts with original findings of a positive effect.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Three-City (3C) Study[e] Samieri, 2008[45]	N: 1,214 community-dwelling adults in Bordeaux, Dijon, and Montepelier France, age 65+ Inclusion: None specified Exclusion: Dementia at baseline	Design: Prospective cohort study Intervention: None; primary independent variable was plasma FA concentration of total n-3 and n-6 PUFA, ALA, EPA, DHA, and docosapentaenoic acid Other independent variables: ApoE-e4 carrier status, various medical risk factors Duration: 4 years	Condition: Dementia Outcomes: Adjusted hazard ratio of incident dementia	Nonadjusted models found significant relationships between a 1-SD increase in plasma levels of total n-3 PFA, EPA, DHA, and n-6:n-3 PUFA ratio and risk of incident dementia. Adjusted models that included ApoE-e4 status found this relationship significant only for EPA; total n-3 PUFA and DHA were significant in ApoE-e4 adjusted models only when interacted with depressive status. Conclusion: Higher plasma EPA is associated with a lower risk of dementia, as are total n-3 and DHA levels in depressed subjects. Comparison to 2005 report: Meets criterion A6, clinically important caveat. Consistent with positive effect findings, but adds new information about ApoE-e4.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Framingham Heart Study Schaefer, 2006[46]	N: 899 subjects, 37% male, mean age 76 years Inclusion: Free of dementia at baseline Exclusion:	Design: Prospective cohort study Intervention: None; primary independent variable was plasma PC DHA level as % of total FA, at baseline Other independent variables: FFQ was also administered to quantify DHA and fish intake; broad range of medical, demographic, BMI, and other variables Duration: 9.1-year mean follow-up to development of dementia/AD	Condition: Dementia Outcomes: Relative risk (RR) of all-cause dementia	Higher levels of plasma PC DHA were associated with a significantly lower RR of dementia but not AD, for those in the top quartile of plasma PC DHA levels compared to the 1st–3rd quartiles. Significance did not rely upon APOE e4 carrier status, adding this variable into the model did not change findings. Mean DHA and fish intake were significantly correlated with plasma PC DHA, based on FFQ report. Conclusion: High plasma PC DHA levels are associated with reduced RR of developing dementia but not AD, independent of APOE e4 status. Comparison to 2005 report: No criteria for change met; consistent with positive effect findings.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Key Question 3 – Treatment of dementia/ Alzheimer's disease (AD)				**2005 Report Conclusion –** -1 study (n=20), some evidence of positive effect -DHA resulted in a small improvement in scores on the MMSE and Hasegawa dementia rating scale
Chiu, 2008[47]	N: 35 subjects in Taiwan, aged 55–90 Inclusion: Mild or moderate AD or amnesiac mild cognitive impairment Exclusion: Inadequate motor or sensory skills to complete testing, depression, mental or substance use disorder, other severe comorbidities, NSAID use. Supplements including fish oil discontinued during study, but subjects with prior fish oil use were not reported.	Design: Randomized, double-blind, placebo-controlled study Intervention: n-3 PUFA capsules (1,080 mg EPA and 720 mg DHA daily) or placebo (olive oil) Other independent variables: Depression Duration: 24 weeks	Condition: AD and mild cognitive impairment Outcomes: Age, group-by-time, and unadjusted mean scores of the MMSE, Clinician's Interview-Based Impression of Change (CIBIC-plus), Alzheimer's Disease Assessment Scale (ADAS-cog), and Hamilton Depression Scale (HDRS)	n-3 PUFA supplementation may improve global cognitive function as measured by the CIBC-plus, relative to placebo, for younger subjects. No associations were found between treatment and placebo groups for the ADAS-cog, MMSE, or HDRS scores. Conclusion: There is limited evidence of a positive effect of n-3 PUFA supplementation on cognitive function. Comparison to 2005 report: No criteria for change met; consistent with small positive effect findings.
Freund-Levi, 2006[48]	N: 174, mean age 74 (SD 9 years) subjects from specialist memory clinics in Stockholm, Sweden Inclusion: AD according to DSM-IV criteria; MMSE score 15–30; living in own home; treatment with stable dose of acetylcholine esterase inhibitors for at least 3 months before start of study and plan to continue treatment for duration of study	Design: Randomized, double-blind, placebo-controlled study Intervention: 4 x 1 g capsules daily for treatment and placebo groups with 4 mg vitamin E in each; active pills had 430 mg DHA and 150 EPA, placebo pills had an isocaloric oil (1 g corn oil, including 0.6 g linoleic acid). Treatment for 6 months, followed by 6 months open treatment with omega-3 fatty acid supplementation in all patients	Condition: Mild to moderate Alzheimer Disease Outcomes: Mean scores on MMSE and cognitive portion of the Alzheimer Disease Assessment Scale (ADAS-COG); global function in Clinical Dementia Rating Scale; safety and tolerability of omega-3 fatty acid supplementation also measured	No significant difference at 6 months between treatment and placebo groups, or at 12 months with both groups receiving treatment, for overall MMSE or ADAS-COG scores. A few specific MMSE items showed positive effects of omega-3 FA treatment, but findings may be spurious. Conclusion: Dietary supplementation with omega-3 fatty acids does not appear to improve cognitive function in patients with mild to moderate AD. This is the only randomized, double-blind,

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Freund-Levi, 2006[48] (cont.)	Exclusion: NSAID use (low-dose acetylsalicylic acid acceptable); use of omega-3 preparations or anticoagulant agents; alcohol abuse; concomitant serious disease; no caregiver.	Other independent variables: Blood and urine analysis, blood pressure assessments Duration: 6 months treatment or placebo, followed by 6 months treatment both groups		placebo-controlled study of omega-3s for treatment of AD known to study authors. Comparison to 2005 report: Meets criterion A7, opposing findings from a non-pivotal trial; negative trend from prior conclusion
Key Question 4 – Incidence of neurological disease (multiple sclerosis, Parkinsons disease, cerebral palsy; excludes dementia)				**2005 Report Conclusion –** -4 studies (n=135,384; 399; 224; and 195), no effect or weak evidence of positive effect -2 studies found no significant effects of omega-3 FA intake on MS incidence, but 1 study found increased fish intake associated with lower MS risk in women -1 study found no significant association between fish consumption, ALA, EPA, or DHA, and risk for Parkinson's disease -1 study found weekly maternal fish intake decreased risk of giving birth to a child with cerebral palsy
Rotterdam Study[†] De Lau, 2005[49]	N: 5,289 subjects from a population cohort in Rotterdam, the Netherlands, of which 51 were in the disease cohort; ages 55+ Inclusion: Independent living, normal cognition Exclusion: Inconsistent reported food frequency questionnaire intake, dementia, parkinsonism at baseline, dementia	Design: Prospective cohort study Intervention: None. Main independent variable was dietary intake at baseline only, using a home-based checklist and dietician-administered FFQ; data converted to n3-PUFAs (ALA, DHA, EPA) Other independent variables: Numerous medical/other variables Study was part of a broad population-based study of disease	Condition: Incident PD Outcomes: Hazard Ratio (HR) of PD in the 51 subjects that developed PD in 6 years	Increased n-3 PUFA intake was associated with a lower HR of PD. For specific n-3 PUFA subtypes, ALA was significant (HR 0.65, 95% CI 0.45-0.95), but DHA and EPA were not. The HR was significant for the overall cohort that developed incident PD during the study's 6-year followup (n=51), but not significant at the specific short and long-term followup intervals (2 and 6 years, n=25 and n=26).

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Rotterdam Study[f] De Lau, 2005[49] (cont.)		Duration: Baseline, 2- and 6-year followup intervals		Conclusion: Higher intake of total n-3 PUFA and ALA may be associated with a lower incidence of PD, although total unsaturated fats are more important. Comparison to 2005 report: Meets criterion A7, opposing findings from a non-pivotal trial. Evidence of a positive effect on incidence of PD; no effect was found in 2005 report.
Miyake, 2010[50]	N: 617 subjects in Japan (249 cases, 368 controls), mean age 68, 37% male Inclusion: Cases were patients within 6 years of onset of PD, controls were inpatients and outpatients without a neurodegenerative disease, but not matched to cases. Exclusion: None specified	Design: Case-control study Intervention: No intervention; primary independent variable was a validated, self-administered diet history questionnaire Other independent variables: Sex, age, region of residence, education, smoking history, BMI, intake of vitamin E, iron, and alcohol Duration: N/A	Condition: Incidence of Parkinson's disease (PD) Outcomes: Crude and adjusted odds ratio of PD	The OR for PD was not significant based on intake of total n-3 PUFAs, ALA, EPA, DHA, or n:3:n-6 PUFA ratio. Conclusion: The study finds no evidence of an association between n-3 PUFAs and PD incidence. Comparison to 2005 report: No criteria for change met. Consistent with no effect findings.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Key Question 5 – Treatment of multiple sclerosis progression				**2005 Report Conclusion –** - 3 studies (n=312, 12, and 16), some/inconsistent evidence of positive effect - 2 studies found a significant reduction in MS disability, one of these reported improvement in disease progression -1 study found omega-3 FA supplement had no effect on disability or relapse rates
Weinstock-Guttman, 2005[51]	N: 27 subjects, age 18–60 Inclusion: Diagnosis of MS, stable disease in past 2 months, 1 or more exacerbations in past 3 years, continued use of normal medications, diet of more than 30% of total calories from fat Exclusion: None specified	Design: Randomized, double-blind, placebo-controlled study Intervention: Low-fat diet for all subjects, 6g fish oil (1.98g EPA, 1.32g DHA) per day treatment group and no more than 15% of total daily calories from fat, vs. 6g olive oil per day for placebo group and no more than 30% of total daily calories from fat Other independent variables: Serum fatty acid concentration of EPA, DHA, and total n-3 PUFAs Duration: 1 year	Condition: MS Outcomes: Quality of life measures – scores on the Primary Component Scale (PCS) and global score of the Short-Form Health Survey (SF-36), Modified Fatigue Impact Scale (MFIS), Mental Health Inventory (MHI); also, immunological parameters.	PCS and MHI improved significantly in the fish oil vs. placebo group at 6 months, but the significant effect disappeared at 12 months; MFIS improved significantly for the placebo group at 6 and 12 months. The global SF-36 score did not change in the fish oil group, and it worsened in the olive oil group, but significance levels were not reported for this outcome. Immunological parameters did not differ significantly between groups at 1 year. Conclusion: Weak evidence of an effect of fish oil supplementation on MS outcomes, but this may also be due to a lower-fat dietary intervention. Comparison to 2005 report: No criteria for change met. Consistent with findings of a weak, possibly positive effect.

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Other – Treatment of Huntington Disease				**2005 Report Conclusion – N/A**
Trial of Ethyl-Eicosapentaenoic Acid in Huntington Disease (TREND-HD) Huntington Study Group - TREND-HD Principal Investigators, 2008[52]	N: 316 (158 in each treatment and placebo groups, 192 completed the study), mean age 53 (SD 10 years), 51% female in Canada and the U.S. Inclusion: Clinical features of HD and either family history or CAG repeat length expansion to confirm HD, 35+ years old, good functional capacity, minimal dystonia, minimal bradykinesia, adequate birth control, ability to take medications orally. Exclusion: Taking exclusionary medications, relevant history of medical/psychiatric/surgical conditions, advanced disease	Design: Randomized, double-blind, placebo-controlled study Intervention: Treatment with ethyl-EPA, 1 g, twice a day vs. placebo (paraffin oil) for 6 months, followed by 6 months treatment for both groups Other independent variables: N/A Duration: 1 year	Condition: HD Outcomes: Primary tests of Total Motor Score 4 (TMS-4) of the Unified HD Rating Scale; numerous other secondary tests of motor skills, cognition, behavior, and function	No difference between treatment and placebo groups on TMS-4, or any secondary tests, in 6 months. At 12 months, those initially randomized to treatment had significantly better TMS-4, chorea score, and total motor score than those initially randomized to placebo; other secondary tests were not significant for differences between groups. Note: Results were publicized after 6 months, leading to drop-out and potential attrition bias – 61% completed the study. Conclusion: Ethyl-EPA was not beneficial for patients with HD during 6 months of placebo-controlled evaluation. Comparison to 2005 report: N/A

Table C1. Effects of omega-3s on cognitive function with aging and on risk for dementia and other neurological disorders (continued)

Article ID / Cohort/First Author/Year	Sample(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Disorder or Condition/ Ascertainment/ Outcome(s) Assessed/	Findings
Puri, 2008[53]	N: 34 subjects, age 30–70 years Inclusion: Symptomatic, genetically confirmed HD or family history of HD at stage I or II; scoring between 50 and 90 for Independence Scale component of Unified HD Rating Scale Exclusion: Use of depot antipsychotic medication	Design: Randomized, double-blind, placebo-controlled study Intervention: 2g/day of ethyl-EPA or placebo (liquid paraffin) Other independent variables: Age Duration: 1 year	Condition: HD Outcomes: Mean change in percentage global brain volume, measured by high-resolution cerebral MRI scans; and Voxel-wise analysis of edge displacement	Global brain volume change and edge displacement by Voxel analysis were significantly better in the treatment than placebo group after the 1st 6 months, but not in the 2nd 6 months or over 1 year. Conclusion: Ethyl-EPA supplementation may offer some benefit for patients with HD. No other drug tested in HD has shown this effect. Comparison to 2005 report: N/A

[a] Same study group as Beydoun 2007, different independent variables (dietary intake in addition to plasma FA), more detailed outcome measure specification also.
[b] This is the same study population as the one study included in the 2005 report (Kalmijn 1997). Van Gelder et al. concluded that "results of the current study differ from [Kalmijn 1997] … in which no clear inverse association between fish consumption and 3-y cognitive decline could be shown. In the current study, we observed a strong inverse association between EPA+DHA intake and cognitive decline. Possible explanations for the discrepancy … could be the longer follow-up period in the current study and the availability of data on the EPA and DHA content of animal and plant foods in addition to fish and seafood."
[c] This is the same study population as one of the studies included in the 2005 report (Kalmijn 1997). The updated study has a longer followup (10 years vs. 2 years), and it conflicts with the earlier study's finding that increased fish intake reduces the risk of dementia.
[d] Similar/overlapping study group as that used by Beydoun (Key Question 1).
[e] Same study cohort as Barberger-Gateau (same Key Question), different independent variable and inclusion criteria.
[f] Same study group used by Devore (Key Question 2).

Cancer Risk and Response to Treatment

Table C2. Effects of omega-3s on cancer risk and response to treatment

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Key Question 1 Effect on tumor incidence **Key Question 1A: What is the evidence that omega-3 fatty acids reduce the incidence of tumors (in humans)? For what type of tumors?**				
All Cancers: **Original report found that "omega-3 fatty acids do not appear to decrease overall cancer risk" based on finding of no effect for most types of cancer**				
Norwegian European Prospective Investigation into Cancer and Nutrition (NEPIC) Engeset, 2009[54]	Part of a larger study (NOWAC) which in turn is part of the larger EPIC 37,212 women enrolled in the NEPIC study Exclusion: possible under- or over-reporting of intake; answering fewer than half the FFQ questions, eating >60 hot meals/month, prevalence of cancer (34,471 remained) Women followed until 1st cancer diagnosis, death emigration, or end of followup period	Prospective Cohort 8-page FFQ/lifestyle questionnaire. Fish intake was considered only for colorectal cancer?	Ascertainment by Cancer Registry of Norway of total cancers, breast cancer, colorectal cancer	Women were characterized according to one of 6 dietary patterns based on FFQ (Fish was one pattern) No overall relationship between cancers and the six different dietary patterns in this study Low intakes of fatty fish were associated with higher risks of cancer only in the context of the Western diet (breast cancer) or high intakes of alcohol (total cancers)
Health Professionals Follow-up Study, US Virtanen, 2008[55]	40,230 US male health professionals 40-75 y at baseline Exclusion: baseline prevalent MI, angina, other heart disease, stroke, or cancer; ≥70 items missing from food frequency questionnaire; reported energy intake <800 or >4200 cal/d	Prospective Cohort Self-administered semi-quantitative validated food frequency questionnaire (FFQ) at baseline and every 4 years asked about intakes of canned tuna (3–4oz serving), dark-meat fish (e.g., mackerel, salmon, sardines, bluefish, swordfish; 3–5 oz/serving); other fish; and shrimp, lobster, or scallops (3.5 oz, but not included in estimates) to estimate EPA and DHA intakes. Fish oil assessed biennially	All cancers except nonmelanoma skin cancer and low-grade organ-confined prostate cancer Self report triggered blinded medical record review; deaths ascertained from relatives, post office, National Death Index; cause of death ascertained from autopsy records, death certificate	Over 18 yrs followup, 4,690 cancer events No significant associations were seen between fish consumption or EPA+DHA consumption and incidence of total cancer, even when comparing the highest with the lowest decile of intake

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Aerodigestive Tract Cancer: Original report identified 1 study (8006 Japanese-American men) that showed no significant effect of fish on the incidence of aerodigestive cancer (Honolulu Heart Program [Chyou 1995]) **No new studies identified**				
Bladder Cancer: Original report identified 1 study (8006 Japanese-American men) that showed no significant effect of fish on the incidence of bladder cancer (Honolulu Heart Program [Chyou 1995]) **No new studies identified**				
Breast Cancer: Original report identified 7 studies (6 cohorts) **Fish consumption (4 studies): 1 study found increased risk in highest vs. lowest quartile of fish intake (n=29,875 Caucasian women); other three studies found no effect (n=120,000; 14,729; 121,700)** **Total and marine n-3 FA (1 study): Highest quartile of marine n-3s had lower risk than women in lowest quartile (n=63,257 Asian women)** **Specific n-3s (1 study): Highest quartile of ALA had lower risk than lowest quartile (n=62,573 men and women[# women unknown])** **No evidence for fish oil, total omega-3s, DHA, or EPA**				
VITAL Cohort Brasky, 2010[56]	35,016 postmenopausal female (50-76 yrs) members of the VITAL cohort, residents of western Washington state Inclusion: response to baseline survey mailed to residents (names purchased from commercial list) Exclusion: Hx of breast cancer at baseline or failure to report on hx; premenopausal or unknown menopausal status. Subsequently women dx w/ in situ breast disease, sarcoma, phyllodes, or lymphoma histology were excluded	Baseline questionnaire on supplement use (herbal and specialty, including mixtures such as multivitamins) in 10 years prior to baseline. Current and past regular use (defined as ≥1day/wk for ≥1 year. Frequency and duration of use measured. (not sure how they explained a supplement or whether they provided a closed-end set from which to choose). Also collected info on other risk factors for BC and correlates of supplement use, ht, wt, physical activity, use of various medications (e.g., NSAIDS), diet (120-item FFQ), Fx hx history of cancer, medical hx, reproductive hx, other lifestyle characteristics	Mean followup time was 6 yrs. Cases ascertained by linking cohort to the regional SEER cancer registry as well as follow-up with area hospitals, pathologists, oncologists, and radiotherapists, and state death certificates	880 eligible cases of invasive BC dx from 1/00 to 12/07. Current use of fish oil was associated with reduced risk of BC (HR, 0.68, 95% CI, 0.50-0.92). 10-yr average use was suggestive of reduced risk (P trend = 0.09). Results held for ductal but not lobular cancers. No other supplement was associated with BC risk. When the interaction of fish oil with other characteristics thought to influence inflammation was examined, current use of fish oil actually increased the risk for BC in those with hx of CAD but decreased BC risk in those w/ no hx of CAD A previous publication reported on validation and reliability of survey for supplement use assessment Conclusion: effect of fish oil inconsistent: decreased risk of DCIS but not LC. Increased risk in those with history of CAD

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
E3N (maybe substudy of EPICS) Thiebaut, 2009[57]	56,007 French women recruited through their teachers' health insurance program Exclusion: participants in the top and bottom 1% of the ratio of reported energy intake to basal metabolic rate; cancer diagnosis (except basal cell skin carcinoma and lobular breast carcinoma in situ); unavailable followup information; use of vitamin E, C or b-carotene supplements in 1995, 2000 or 2002, (leaving 56,007 subjects).	Dietary questionnaire 8 years of followup	Ascertainment by fx report, postal service, and by searching the health insurance company (MGEN) database. Information on cause of death was obtained from the National Service on Causes of Deaths (INSERM CepiDC).	1,650 women developed invasive breast cancer. Breast cancer risk was not related to any dietary PUFA overall; Breast cancer risk was inversely associated with α linolenic acid (ALA) intake from fruit and vegetables [highest vs. lowest quintile, hazard ratio (HR) 0.74; 95% confidence interval (CI) 0.63, 0.88; p trend < 0.0001], and from vegetable oils (HR 0.83; 95% CI 0.71, 0.97; p trend 0.017). Conversely, breast cancer risk was positively related to ALA intake from nut mixes (p trend 0.004) and processed foods (p trend 0.068), as was total ALA intake among women in the highest quintile of dietary vitamin E (p trend 0.036). A significant interaction was also found between n-6 and long-chain n-3 PUFAs, with breast cancer risk inversely related to long-chain n-3 PUFAs in women belonging to the highest quintile of n-6 PUFAs (p interaction 0.042). Conclusion: Effects of ALA inconsistent, depending on food source
National Cancer Center Hospital, Korea Kim, 2009[58]	979 (362 cases, mean age 48.3; 617 controls, mean age 47.9) women/ Inclusion: Dx breast cancer (BC) Exclusion: prior history of cancer; inability to be interviewed; implausible daily energy intake Matched on age±5 years	Case control FFQ: 8 fish items used to estimate quartiles of intake of lean fatty, total fish, DHA, EPA	Breast cancer diagnosed at cancer center Adjusted odds rations (age, multivariates) for quartiles of intake in pre- and post-menopause	Intakes of fatty fish were associated with a decreased risk of BC in pre- and postmenopausal women (highest vs. lowest quartiles of intake BC risk decreased in postmenopausal women who consumed >0.101g/d EPA and 0.213g/d DHA from fish compared to the reference group (<0.014g/d EPA, 0.037g/d DHA)

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
National Cancer Center Hospital, Korea Kim, 2009[58] (cont.)				BC risk decreased in premenopausal women for highest vs. lowest quartile of intake of total n-3 FA Conclusions: results suggest high consumption of fatty fish ∝ reduced BC risk and that n-3 FA intake 1/∝ BC risk
Shanghai Textile Industry Bureau cohort Shannon, 2009[59]	Women born between 1925 and 1958, permanent residents of Shanghai from breast self-exam trial; 622 women developed fibrocystic changes and 432 developed breast cancer (336 completed FFQ)	Case control Questionnaire completed between 1989 and 1991. Monitored through 2000 for breast changes Food frequency questionnaires administered to a subset of women Tissues analyzed by 2 pathologists independently Red blood cell fatty acids analyzed	Proliferative and non-proliferative fibrocystic disease and progression to breast cancer: tissue analysis in duplicate	Women in the highest quartiles of EPA erythrocyte concentration were 67% less likely to have nonproliferative changes alone or with breast cancer and 49% less likely to have breast cancer than women with proliferative changes (or than women in the lowest quartiles?). Total n-3 PUFAs and EPA were associated with a significant reduction in risk of NPFCs alone; total n-3s, EPA and DHA were associated with a significant reduction in risk of breast cancer in women with nonproliferative changes cf. controls. Ratio of palmitic to palmitoleic also associated with decreased risk for all conditions, suggesting ð-9 desaturase may be of greater importance than FA levels alone. Conclusion: n-3s in all forms associated with risk reduction, but evidence suggests indirect effect.

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Shanghai Textile Industry Bureau cohort Shannon, 2007[60]	Women born between 1925 and 1958, permanent residents of Shanghai from breast self-exam trial; 322 BC cases included	Case control Questionnaire completed between 1989 and 1991. Monitored through 2000 for breast changes Food frequency questionnaires administered to a subset of women Tissues analyzed by 2 pathologists independently Red blood cell fatty acids analyzed	Breast cancer dx confirmed at one of 3 hospitals used by the bureau	% n-3 PUFA associated with significantly lower risk of BC, primarily attributable to EPA. Data suggest importance of ratio of monounsaturated to saturated fatty acids Conclusions: n-3s decrease risk of BC
EPIC Engeset, 2006[61]	310,671 women aged between 25 and 70 yr	dietary questionnaire between 1992–98 Median followup of 6.4 yr	Ascertainment based on population cancer registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the UK and on a combination of methods, including health insurance, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin in France, Germany, and Greece	Hazard ratio for breast cancer by intake of total and lean and fatty fish were estimated, stratified by study centre and adjusted for established breast cancer risk factors. During follow-up, 4,776 invasive incident breast cancers were reported. No significant associations between intake of total fish and breast cancer risk were observed, hazard ratio (HR) 1.01 (95% confidence interval [CI] 0.99–1.02; p=0.28 per 10 g fish/day). When examining lean and fatty fish separately, we found a ***positive significant association only in the highest quintile for fatty fish*** (HR 1.13, 95% CI 1.01–1.26), but test for trend was not significant (p =0.10. No difference was seen between pre- and postmenopausal women Conclusions: no effect or positive effect of fish/fatty fish intake on BC risk

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Japan Collaborative Cohort Study (JACC) Wakai, 2005[62]	26,291 women aged 40–79 years Participants were enrolled from 45 study areas throughout Japan, from general populations or participants in municipal health check-ups	Prospective cohort Questionnaire on dietary and other factors completed at baseline (1988 to 1990) Mean follow-up of 7.6 years	Ascertainment of the incidence of cancer by means of a linkage with the records of population-based cancer registries, supplemented by a systematic review of death certificates	129 breast cancer cases were documented during followup period. Significant decrease in risk was detected for the highest quartile of intake compared with the lowest for fish fat and long-chain n-3 fatty acids; the RR were 0.56 (95% CI 0.33– 0.94) and 0.50 (0.30–0.85), respectively Conclusions: marine and non marine n-3s associated with decreased risk BC
Iowa Women's Health Study Cohort Folsom 2004[63]	41,836 women (55-69 yoa) recruited via baseline mailed questionnaire	Prospective cohort Single baseline 127-item FFQ used 4 questions to assess intakes (servings and frequencies) of 1) dark meat fishes (3-5 oz), 2) canned tuna (3-4 oz), 3) other fish (3-5 oz), 4) shrimp, scallops, or lobster (3.5 oz) and calculated average daily intake of omega 3s. No questions about fish oil. Assessment of cancer incidence and deaths for 11 years (using mailers and linkage to state-wide records)	Deaths, breast cancer incidence in relative risk	Baseline fish consumption was similar to that of most contemporary U.S. populations. Conclusion: Neither fish intake nor marine omega 3s intake were associated with incidence of breast cancer.

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Malmö Diet Cancer (MDC) Cohort Wirfält, 2004[64]	17, 035 women born between 1923 and 1950 and living in Malmö in 1991. Potential participants were sent letters or joined spontaneously; for this analysis, only postmenopausal women were included (defined as women over 50, n=12, 039) Exclusion: prevalent breast or other cancer (except cervical cancer in situ or non-melanoma skin cancer); limited Swedish language skills	Nested Case control Diet hx obtained by interviewers using 7-day menu book completed by participants at home and a questionnaire assessing the previous year. Data entered into MDC food and nutrient database. Reproducibility and concurrent validity assessed previously Erythrocyte membrane n-3 values were measured in blood samples	Ascertainment of breast cancer by record linkage with Swedish Cancer Registry and Southern Swedish Regional Cancer Registry	249 incident breast cancer cases, resulting in 237 case control sets (exclusion for other prevalent cancer) Dietary n-3s were positively correlated with erythrocyte membrane fatty acids but no difference was seen in erythrocyte FA from fish and breast cancer risk Conclusion: erythrocyte membrane n-3 FA not associated with BC risk
Summary for Breast Cancer: 8 new studies (>100% increase in number of studies) with more than 50% increase in number of participants, total. 1 pivotal study (by size) shows potential detrimental effect of fatty fish. Other smaller studies show decreases risk or no link.				
Colorectal Cancer **Original report identified 6 studies (6 cohorts):** **Fish consumption (4 studies): 1 study found decreased risk in highest vs. lowest quartile of fish intake in 1 study (n=14,727 women); other three studies found no effect (n=47,949 men; 3,111 men and women; 88,751 women)** **Total n-3 FA (1 study): Highest quartile of n-3s had nonsignificantly lower risk than women in lowest quartile (n=35,215 Caucasian women)** **Specific n-3s (1 study): No difference for any n-3 (n=61,483 Caucasian women)**				
Singapore Chinese Health Study Butler, 2009[65]	63,257 men and women recruited between April 1993 and December 1998, from permanent residents or citizens of Singapore aged 45–74 years, and who resided in government-built housing estates (most citizens reside in such housing) Inclusion: baseline interview/questionnaire completion Exclusion: prior cancer 61,321 enrolled	Prospective cohort Validated 165-item FFQ w/ 14 fish items, all known to be lean fish; intake corrected for energy intake	Ascertainment by record linkage of the cohort database with respective databases from the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths	As of December 31, 2005, 961 incident colorectal cancers reported Hazard ratios for highest vs. lowest quartiles of marine n-3 and saturated fat consumption. Marine n-3 polyunsaturated fatty acid (PUFA) intake was *positively* associated with advanced disease (Dukes C or D) (HR = 1.33, 95% CI = 1.05–1.70, *p* for trend = 0.01), regardless of sex. The association with marine n-3 PUFAs was strongest among those with the shortest (≤5 years) duration of follow-up (HR = 1.49, 95% CI = 1.00–2.21, *p* for trend = 0.04). In contrast, we observed a small, albeit

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Singapore Chinese Health Study Butler, 2009[65] (cont.)				imprecise, *inverse association* with marine n-3 PUFAs for localized colorectal cancer among those with the longest duration of follow-up (>10 years) (HR = 0.62, 95% CI = 0.29–1.34, *p* for trend = 0.55)
Cancer Prevention Study-II Nutrition Cohort Daniel, 2009[66]	99,080 participants (43,108 men and 55,972 women) Population described here: Cancer 2002;94:2490 – 501	Baseline questionnaire in 1992,1997, 1999, 2001, 2003, and 2005 1999: 152-item FFQ No questions about use of flax or fish oil, only dietary intake was considered. Queries regarding the frequency of seafood intake included canned tuna fish, dark-meat fish (mackerel, salmon, sardines, bluefish, and swordfish), other fish (cod, haddock, and halibut), shellfish (shrimp, lobster, scallops, and clams), and breaded fish (fish sticks, cakes, or pieces).	Reported cancers were verified through medical records, registry linkage, or death certificates	869 incident colorectal cancer cases (452 men and 417 women) Ratio of total n-6 to total n-3 intake was not associated with colorectal cancer risk in either sex. Total n-6 intake was inversely related to colorectal cancer risk in men [multivariate relative risk (95% confidence interval) for highest to lowest quartile, 0.81 (0.61-1.07); Ptrend = 0.07], and *α*-linolenic acid, the primary contributor to total n-3 intake, was associated with increased risk in women for quartiles 2 through 4 versus the lowest quartile [relative risk (95% confidence interval), 1.50 (1.12-2.01), 1.40 (1.04-1.87), and 1.38 (1.02-1.85), respectively; Ptrend = 0.13]. In women, total n-6 and marine n-3 intake appeared to be associated with higher and lower risk, respectively, but associations were attenuated with adjustment for other risk factors

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
FISHGASTRO: Wageningen Netherlands and Norwich UK Pot, 2009[67]	Individuals 18-80 recruited fr 2004-2007; 242 participants (216 completed) 3 sets inclusion criteria (3 difft groups): (1) those with hx of colorectal polyps; (2) those with dx of UC (inactive); (3) those w/ no macroscopic sign of colon disease (attended clinic for IBS, hemorrhoids, unexplained anemia, bowel complaints, or changes in defecation patterns); 10% participation rate (mainly due to unwillingness to increase fish intake or undergo add'l sig) Exclusion criteria: fish allergy, taking fish oil supplements; taking NSAIDS or aspirin, organ transplant recipients, receiving immunosuppressive therapy; Type 1 DM, increased risk infection	Multicenter RCT w/ 3 arms: 1) oil-rich fish group (2x150g salmon/wk); 2) lean fish group; 3) dietary advice group for 6 months. Patients given fish and asked to incorporate into diet in addition to any fish normally eaten. Compliance checked with food diaries, regular phone calls, and for the salmon group, serum n-3 VLC-PUFA concn.	Baseline and post-intervention colonoscopy and biopsy Histological confirmation of polyps Fasting blood cholesterol, vitamin D, selenium FFQ and food diary Primary outcome = crypt cell apoptosis and proliferation in colonic biopsy samples	Jadad score 3 (assessors but not participants blinded) Additional fish consumption of ~1.4 servings /wk (either oily or lean) over 6 months did not significantly change apoptotic and mitotic rates of the colon mucosa (i.e., proliferation, associated with risk for cancer) in a population of fish eaters
Physicians' Health Study Hall, 2008[68]	See Hall, 2007 below	Prospective cohort study Fish intake assessed at 12-month followup using an abbreviated semiquantitative food-frequency questionnaire validated in a similar population. Asked about intakes of 4 types of fish 22-year followup	See Hall, 2007[68]	At 22-yr followup, 500 confirmed cases of CRC Fish intake was inversely associated with colorectal cancer risk [multi-variate relative risk (95% confidence interval) for highest versus lowest category, 0.60 (0.40–0.91); Ptrend = 0.01]. The inverse association was observed for both colon and rectal cancers. Findings for n-3 fatty acids were similar to those for fish; the multivariate relative risk (95% confidence interval) of total colorectal cancer for the highest versus lowest quartile of n-3 fatty acids was 0.74 (0.57–0.95; Ptrend = 0.01)

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
SOCCS (Study of Colorectal Cancer in Scotland) Theodoratou, 2007[69]	2910 cases and controls (1,455 each, males and females) prospectively recruited from 1999-2006 among all 16-79 year olds diagnoxed with adenocarcinoma of colon in Scottish hospitals Exclusion: death prior to ascertainmnt, being too ill to participate, case represented recurrence; inability to give informed consent	Case control study Semi-quantitative 150-item FFQ; health, lifestyle questionnaire/hx Fatty acid composition of food obtained from UK food composition tables and compared in cases vs. controls	Ascertainment in hospitals; recruitment within 2–3 mos of dx to limit survival bias	Multiple logistic regression models showed EPA, DHA, and EPA+DHA/ALA were inversely proportional to adjusted OR for developing colorectal cancer in **dose-dependent** manner. Relationships persisted even after adjustment for energy intake
Geelen, 2007[70]	Meta-analysis of 19 prospective cohort studies (only 6 included in original omega 3s report – 11 clearly missed based on publication date; not sure why; possibly due to rejection at title stage due to apparent lack of relevance) two newer studies	**Meta-analysis** Pooled relative risks in highest vs. lowest category of exposure for fish intake and derived omega 3 fatty acids	Colorectal cancer incidence and mortality	Pooled relative risks for highest vs. lowest fish consumption category (14 studies): 0.88 (95% CI, 0.78, 1.00); for colorectal cancer mortality (4 studies): 1.02 (95% CI 0.90 1.16) For each extra occurrence of fish consumption/wk, pooled relative risk was 0.96 (0.92, 1.00) Effect more pronounced for women than men and in studies w/ larger difference between highest and lowest exposures
Physicians' Health Study Hall, 2007[71]	178 male participants diagnosed with CRC during followup (through 1995) 1-2 controls selected from unaffected members of cohort (with no cancer at time case reported cancer) for each case (104 cases had two controls), matched for age and smoking status	Nested case control using blood samples Annual followup questionnaires	Cases reported on annual questionnaires were followed up with patients' physicians	Total long-chain n-3 fatty acids were non-significantly inversely associated with CRC risk [relative risk (RR) for highest versus lowest quartile, 0.60; 95% confidence interval (95% CI), 0.32 to 1.11; Ptrend = 0.10], after adjustment for possible confounders. Potential interaction was seen between randomized aspirin assignment and long-chain n-3 fatty acid levels (Pinteraction = 0.04).

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample#(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Physicians' Health Study Hall, 2007[71] (cont.)				Among men not on aspirin, RRs (95% CI) for increasing quartiles of long-chain n-3 fatty acids were 1.00 (reference), 0.60 (0.28-1.28), 0.51 (0.22- 1.17), and 0.34 (0.15-0.82), Ptrend = 0.006. For participants taking aspirin, there was no additional benefit of increasing n-3 fatty acid levels. RR (95% CI) for the highest versus lowest quartile of n-6 fatty acids was 0.64 (0.35-1.17) Conclusion: long-chan n-3 FA clearly decreased CRC in men not taking aspirin
EPICS (European Prospective Investigation into Cancer and Nutrition) Norat et al., 2005[72]	478,040 men and women (mostly age 35–70 years) from 23 centers in 10 European countries who were free of cancer at enrollment between 1992 and 1998. Participants were mostly recruited from the general population with the exception of a group of women teachers who were recruited through their health insurance pool in France and women in Utrecht who were recruited during breast cancer screening. Exclusion: prevalent cancer other than nonmalignant skin cancer; energy intake at the high or low extreme end	Prospective cohort study mean followup of 4.8 years Diet over the 12 months prior to enrolment was assessed using validated country-specific questionnaires. Fish included fresh, canned, salted, and smoked fish 8% random sample of the cohort (36 994) also received a detailed computerized 24-hour diet recall	Colorectal cancer incidence; ascertainment based on population cancer registries, except in France, Germany, and Greece, where a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next-of-kin was used. Mortality data were collected from either the cancer or mortality registries at the regional or national level	1329 incident colorectal cancers were documented Intake of fish was statistically significantly inversely associated with colorectal cancer risk (for highest versus lowest intake HR = 0.69, 95% CI = 0.54 to 0.88, *P*trend<.001). The trend for an inverse association was statistically significant for cancers of the left side of the colon (*P*trend = .02) and the rectum (*P*trend<.001), but not for cancers of the right side of the colon. The hazard ratios per 100-g increase in fish intake were 0.70 (95% CI = 0.57 to 0.87, *P*trend<.001) and 0.46 (95% CI = 0.27 to 0.77, *P*trend = .003) before and after correction. The association was statistically significant and similar for both colon and rectal cancers. Fish effect was not consistent across all centers. In this study population, the absolute risk of development of colorectal cancer within 10 years for

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
EPICS (European Prospective Investigation into Cancer and Nutrition) Norat et al., 2005[72] (cont.)				a study subject aged 50 years was 1.86% for subjects in the lowest category of fish intake and 1.28% for subjects in the highest category of fish intake.
The JACC (Japan Collaborative Cohort Study for the Evaluation of Cancer Risk) Study Kojima, 2005[73]	65,184 of the 110,792 study participants living in 24 study areas with cancer registries. 169 incident colorectal cancer cases and 481 controls Exclusion: previous hx of cancer	Nested case control Relative risk of colorectal cancer development cf. quartiles of serum fatty acids	Case ascertainment used population-based cancer registries supplemented with death certificates	Total n-3s were inversely associated with colorectal cancer risk: Risk reduction 76% cf Q4 to Q1 (OR 0.24, 95% CI 0.08, 0.76) p for linear trend 0.08 In men: ALA: OR 0.39 (95% CI 0.16, 0.91) DPA: OR 0.30 (95% CI 0.11, 0.80) DHA : OR 0.23 (95% CI 0.07, 0.76) Link between DPA and cancer for women was weak and nonsignificant
Swedish Mammography Cohort Larsson, 2005[74]	61,433 women aged 40-75 years and free from diagnosed cancer at baseline in 1987-1990	Cohort study FFQ Mean followup of 13.9 years,	Relative risk of colorectal cancer	Identified 234 proximal colon cancers, 155 distal colon cancers and 230 rectal cancers. No association was seen with fish intake and CRC at any site in the colon
Women's Health Study Lin, 2004[75]	39,876 women ≥45 recruited beginning in 1993 Exclusion for this analysis (2,329): provision of inadequate dietary information at baseline, implausible total energy intake , or lack of information on potential risk factors at baseline 202 incident cases over 8.7 years among the 37,547 participants	Cohort based on WHS RCT (a trial of low dose aspirin and vitamin E) 131-item FFQ Followup questionnaires every 6 months for 1 year and yearly thereafter Intakes of dietary fat and fatty acids were categorized into quintiles	Medical records and pathology reports for incident cases and reported deaths	Multivariate analysis, Cox proportional hazards regression used to estimate relative risks. No association was seen between intakes of any type of fat (including n-3s) and total fat and risk for colorectal cancer in these women (however intake of fried foods showed some association)

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Summary for CRC: 8 new studies with more than 50% increase in number of participants, total. Some studies supported finding of decreased risk with increased fish intake. New support for decreased risk with individual n-3s.				
Lung Cancer: Original report identified 3 studies (3 cohorts) that assessed effect of n-3s on incidence and 1 that assessed effect on mortality 1 study found decreased risk with highest vs. lowest tertile fish intake; other studies found no effect of higher fish consumption on incidence or death No new findings				
Lymphoma: Original report identified 2 studies (2 cohorts) on incidence of non-Hodgkins lymphoma (NHL) Fish intake:1 study found no effect of increasing fish consumption (35,156 women) Total n-3s: 1 study found no effect of increasing intake of n-3s (as % total caloric intake) (88,410 women)				
Scandinavian Lymphoma Etiology (SCALE) study Chang, 2006[76]	Newly diagnosed malignant lymphoma patients and controls in Sweden and Denmark Dietary study involved residents 18-74 yoa of 7 Swedish counties (10/00-4/02) Inclusion: no hx of organ transplantation, human immunodeficiency virus infection, or prior hematopoetic malignancy; ability to communicate in Swedish; first, incident morphologically verified dx NHL (811 cases/686 consented to participate/614 completed diet questionnaire); controls (576 of 718/492 completed diet questionnaire) were identified in general population by computerized register (New sample every 6 months matched to expected 10-year age group and sex of cases	Population-based case control study Semi-quantitative validated FFQ measured average daily consumption of total omega 3s and marine fatty acids	Rapid case ascertainment system established for this study w/ backup of nationwide cancer registry	Dietary intake of omega 3s or marine fatty acids was associated with decreased risk NHL and chronic lymphocytic leukemia. Comparing highest and lowest quartiles of marine fat intake, OR for NHL risk was 0.6 (95% CI, 0.4, 0.9)(ρ trend=0.03)

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Ovarian Cancer **Original report identified one study that assessed the effect of various kinds of fat, including n-3s, on incidence and found no effect** **No new studies found**				
Pancreatic Cancer **Original report identified two studies (two cohorts)** **Fish consumption (1 study): no significant effect of fish consumption (27,111 men)** **Total n-3 consumption (1 study): no effect of n-3s** **ALA (2 studies): no effect of ALA)27,111 men; 88,802 women)** **No new studies**				
Prostate Cancer: **Original report identified 7 studies (5 cohorts)** **Fish consumption (4 studies): 1 study showed inverse effect (6,272 men); one study showed positive effect (14,000 7th day Adventists); other two studies (total 56,763) showed no effect** **Marine n-3s (1 study): no effect found (47,855 health professionals)** **DHA and EPA (two studies): no effects seen (approx. 108,000)** **ALA (3 studies): increased risk for advanced cancer but not overall (47,866) in one study; no significant effect in the other (58,279) (data missing for 3rd)**				
Simon, 2009[77]	16 studies assessing effect of ALA on risk for prostate cancer; studies that compared highest and lowest quintiles were pooled	**Systematic Review** of studies that reported ORs, RRs, or relative hazards and 95% CIs	Prostate cancer / ascertainment unclear	Studies suggested a slight increase risk for prostate cancer with increased ALA. New studies, retrospective case control studies, and studies that assessed ALA intake by inferring from blood levels tended to identify a small effect whereas older studies, prospective cohort, and dietary assessment studies tended to see no effect.

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Physician's Health Study Chavarro, 2008[78] (earlier version included in Simon MA[77])	22,071 male physicians aged 40-84 enrolled in 1982 in a trial of aspirin and beta carotene to prevent heart disease and cancer. 2,161 men were dx w/ prostate ca during the followup. Excluded from analysis were men who did not repot fish intake or who died or reported a cancer Dx prior to the 12-month followup period. Men were followed until date of cancer dx, death, or end of followup (3/1/06), whichever came first.	Prospective study of fish intake using trial population. 12-month Questionnaires (abbreviated FFQ) assessed average intake of 4 classes of fishes over previous year but did not allow estimation of total energy intake Fish and seafood n-3 FA intakes were also corroborated with blood EPA and DHA in 436 members of cohort (controls)	Dx ascertained and stage, grade, etc. confirmed by hospital records and pathology reports. Most cases initially dx by PSA screening.	Total fish intake as well as specific types of fish intake (except "Other") were unrelated to prostate cancer dx (incidence). This lack of relationship was not affected by baseline BMI or assignment to aspirin or beta carotene treatment. However, among those who died, baseline fish intake was inversely related to prostate cancer mortality for all types of fish except shellfish, even after omitting those diagnosed by PSA (men assumed to be more health conscious and detected early).
Physicians' Health Study Chavarro, 2007[79] (included in Simon MA[77])	See above	Nested case control among 14,916 apparently healthy men; whole blood levels of PUFAs determined in 47 men diagnosed with PC during 13-year followup and matched controls	Total PC, stage (nonaggressive, aggressive, subsequent metastases, death)	**Whole blood levels** of all LC n-3 FA (mainly found in marine foods) were inversely correlated with overall risk of PC (RR quintile 5 vs. 1=0.59 [0.38, 0.93], p trend=0.01); linoleic acid was also inversely related ALA was unrelated to PC risk
European Prospective Investigation into Cancer and Nutrition (EPIC) Crowe, 2008[80]	962 men dx w/ prostate cancer after median followup time of 4.2 yrs and 1,061 matched controls participating in EPIC	Nested case control analysis Validated FFQ	Population-based cancer registries in 6 of the participating countries; in Germany and Greece, followup was via self-completed questionnaire and medical records	**Plasma levels of EPA and ALA** were positively associated with risk of high-grade prostate cancer but relationship between EPA, DHA, and ALA and risk of prostate cancer in general were not significant
European Prospective Investigation into Cancer and Nutrition Crowe, 2008[81]	After median followup of 8.7 years, 2,727 men dx w/ prostate cancer in EPIC.	Nested case control analysis Validated FFQ	Population-based cancer registries in 6 of the participating countries; in Germany and Greece, followup was via self-completed questionnaire and medical records	Age-standardized PC incidence differed 6-fold by country (Sweden highest; Greece lowest) Fat intakes differed x 11%. No relationship was seen between intake of any type of fat (total, PUFA, MUFA, saturated, P/S ratio, red and processed meat, dairy, fish) and prostate cancer incidence

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample#(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Multiethnic Cohort Study Park, 2007[82] (included in Simon MA[77])	>215,000 men and women in L.A. and Hawaii ≥45 yoa in original study 82,483 men in this analysis Inclusion: membership in 1of 5 ethnic groups Exclusion: previous prostate cancer Dx, invalid dietary information, missing information on height, weight, educational level, smoking status	Prospective cohort Questionnaire on diet and health history	Incident cases identified by linkage to 3 SEER-linked cancer registries	Overall, study found no evidence for a link between total n-3s, ALA, DHA, EPA and prostate cancer link. Trend toward a protective effect of total n-3s on prostate cancer in Latino and white men but not blacks or Japanese Americans
Miyoko Study Pham, 2007[83]	5,589 men aged 30–79 years in 4 areas of Fukuoka Prefecture Japan. Enrollment was from ’86-’89 and men followed to ’99 or ‘03	Prospective cohort study FFQ used to classify participants into low and high fish intake (Fish intake was assessed at the five levels of ‘twice or more per day’, ‘once a day’, ‘2–4 times per week’, ‘2–4 times per month’ and ‘seldom or never’. For the present analysis, consumption levels were converted into two groups by combining the ‘2–4 times per month’ and ‘seldom or never’ groups into a new ‘low intake’ group; and the ‘twice or more per day’, ‘once a day’ and ‘2–4 times per week’ groups into a ‘high intake’ group)	Risk of death from prostate cancer; ascertainment from death certificates	Cox proportional hazards model Consistent inverse association of this cancer with higher intakes of fish. The multivariate model adjusted for potential confounding factors and some other food items showed a HR of 0.12 (95% CI 0.05, 0.32) for the high intake group of fish consumption.

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Cancer Prostate in Sweden (CAPS) Hedelin, 2006[84] (Included in Simon MA[77])	Swedish men age 35–79	Case control study 261-item validated FFQ	National Prostate Cancer Registry	1,130 controls, 1,499 cases Dietary marine n-3s from fatty fish associated with decreased risk PC (OR for fatty fish ≥1/week vs. never 0.57 CI 0.43, 0.76; OR highest vs. lowest quartile marine FA 0.70, CI 0.51, 0.97) Significant interaction with small nuclear polymorphism in COX-2 gene (key enzyme in eicosanoid synthesis, over-expressed in PC tissue) but not with 4 other SNPs
PLCO Cancer Screening Trial Koralek, 2006[85](Included in Simon MA[77])	29,592 eligible men primarily Caucasian Exclusion: previous history of cancer except melanoma, incomplete baseline and dietary survey information	Prospective cohort study 137-item semi-quantitative FFQ	PSA screening results and annual questionnaires were followed up with medical record reviews as well as review of pathology/autopsy reports,	1,898 cases of prostate cancer (1,631 organ-confined and 285 advanced stage); ALA intake was not associated with overall risk for prostate cancer (multivariate RR for highest vs. lowest quintiles: 0.94 (0.81, 1.09), organ confined or advanced prostate cancer. Also, ALA from specific foods was not associated with prostate cancer risk.
Bidoli, 2005[86] (Included in Simon MA[77])	1,294 Italian men with prostate cancer in 5 areas of Italy Controls were 1,451 male inpatients admitted to same hospitals for conditions unrelated to malignancy or dietary modification	Case-control study Health questionnaire included FFQ	Histological ascertainment by major regional teaching or general hospital	Multiple logistic regression models showed that highest quintile of ALA consumption was associated with a lower risk of PC compared with the lowest quintile(OR 0.7, 95% CI 0.6, 0.9) and a significant trend with increasing consumption, but decreasing ALA risk was also associated with increasing linoleic acid (n-6) consumption.

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Summary for Prostate Cancer: 9 new studies (7 cohorts) and MA suggests need for update. Findings remain contradictory with some showing positive, some negative, and some no association				
Renal Cancer **No studies in original report**				
Alpha-Tocopherol Beta-Carotene Cancer (ATBC) Prevention Study (Finnish cohort of smokers) Wilson, 2009[87]	228 renal cell CA cases diagnosed among 27,111 Finnish males who smoked ≥5 cigarettes/d and or whom dietary information was available Exclusion: prior cancer Hx except nonmelanoma or carcinoma in situ; severe exertional angina, chronic renal insufficiency, cirrhosis of the liver; alcoholism, anticoagulant use, vitamin E (>20mg/d), vitamin A (>20,000IU/d), beta-carotene (>6mg/d) or other problems perceived to limit participation over 6 years	Original design RCT of vitamin A supplementation and lung cancer/Nested case control (?) Baseline self-administered FFQ assessed intake of frozen fish, rainbow trout, Baltic herring, other fresh fish, canned/salted fish	Renal cell cancer/ascertained by ATBC and Finnish cancer registry dual record review	Hazard (risk) ratio for RCC was not associated with intakes of any fish except Baltic herring; highest quartile of intake was associated with increased risk of RCC
Swedish Mammography Cohort Wolk, 2006[88]	Of 66,651 women who completed the baseline questionnaire, 150 incident cases of renal cell carcinoma (RCC) dx in 15.3 mean yrs followup	Validated 67-item FFQ at baseline and 96-item FFQ in 1997 asked about servings per week of fatty fish, lean fish, and other seafood (shellfish)	Ascertainment through computerized linkage with national and regional cancer registers	In age-adjusted and multivariate analyses, fatty fish consumption of ≥1 serving/week was associated with a significant 44% decreased risk of RCC. No association was found for lean or other fish. Sensitivity analysis was carried out for decades of followup. Women who consistently reported long-term consumption of ≥1-3 servings of fatty fish/month at baseline and 10 yrs later had a 74% lower risk of RCC cf. no consumption.

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Skin Cancer: **Original report found 1 study that looked only at basal cell carcinoma. Highest n-3 consumption associated with small but significantly increased risk of BCC relative to lowest quartile. (43,217 health professionals)**				
Community-based study in Australia Hughes, 2009[89]	Randomly selected group from among 1,621 adult participants in a skin cancer prevention trial Exclusion: at least 1 indeterminate actinic keratosis (AK), answering <90% FFQ, energy intake outside the normal limits	RCT cf beta-carotene supplementation and sunscreen Validated 129-item FFQ administered in '92, '94, '96 (participants chose one of 9 responses [never-4+times/d] for how often they'd eaten a given amount of each of the foods)	Outcome was AK (pre-malignant skin tumors/lesions) assessed by experienced dermatologists at 14 separate body sites (cts>50 called indeterminate)	Strongest association between food and AK was that for oily fish. Between 1992 and 1996, AK increased by 95% in those with the lowest intakes , 45% among those with intermediate intake (1serving/2 weeks, on average), and 41% among those with the highest (fully adjusted) intakes (1 serving/5 d). Prevalence decreased by 26% and 28%, respectively. Sensitivity analysis looking only at those without daily sunscreen use found that AK acquisition was not related to intermediate level of oily fish intake, but high oily fish intake remained strongly (negatively) associated with AK acquisition (RR: 0.66, 95%CI, 0.45, 0.98)compared with the lowest intake
Stomach Cancer: **Original report identified 1 study that assessed risk relative to fish consumption and found no effect.** **No new studies**				
KQ 1B: If omega-3 fatty acides influence the incidence of tumors, is there an inverse relationship with intake? **Original report identified the following dose effects** **Breast cancer: dose effects for marine n-3s and ALA; no dose effects for fish, total n-3s, DHA, EPA** **Colorectal cancer: dose effects tested but not observed** **Lung cancer: study that reported reduced risk of CA reported dose effect** **Lymphoma: dose effects tested but not observed** **Ovarian cancer: no dose effects observed** **Pancreatic cancer: dose effects tested but not observed** **Prostate cancer: Dose effects tested in all 7 studies. Dose effects seen for fish in two of four studies, but in opposite directions. Dose effects seen for ALA in two studies but in opposite directions. No dose effect seen for EPA, DHA, total n-3s.** **Skin cancer: Study found increased risk with increasing dose.** **Stomach cancer: dose response assessed but not seen**				

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
SOCCS (Study of Colorectal Cancer in Scotland) Theodoratou, 2007[69]	2910 cases and controls (1,455 each, males and females) prospectively recruited from 1999-2006 among all 16-79 year olds diagnoxed with adenocarcinoma of colon in Scottish hospitals Exclusion: death prior to ascertainmnt, being too ill to participate, case represented recurrence; inability to give informed consent	Case control study Semi-quantitative 150-item FFQ; health, lifestyle questionnaire/hx Fatty acid composition of food obtained from UK food composition tables and compared in cases vs. controls	Ascertainment in hospitals; recruitment within 2–3 mos of dx to limit survival bias	Multiple logistic regression models showed EPA, DHA, and EPA+DHA/ALA were inversely proportional to adjusted OR for developing colorectal cancer in dose-dependent manner. Relationships persisted even after adjustment for energy intake
The JACC (Japan Collaborative Cohort Study for the Evaluation of Cancer Risk) Study Kojima, 2005[73]	65,184 of the 110,792 study participants living in 24 study areas with cancer registries. 169 incident colorectal cancer cases and 481 controls Exclusion: previous hx of cancer	Nested case control Relative risk of colorectal cancer development cf. quartiles of serum fatty acids	Case ascertainment used population-based cancer registries supplemented with death certificates	Total n-3s were inversely associated with colorectal cancer risk: Risk reduction 76% cf Q4 to Q1 (OR 0.24, 95% CI 0.08, 0.76) p for linear trend 0.08
KQ 1c: Is there a temporal relationship with intake? The original report identified no studies that answered this question, and no new studies were identified that addressed this question.				
KQ1d: What is the evidence that genes involved in omega-3 fatty acid transport or metabolism influence the magnitude or direction of the influence on tumor incidence? The original report identified no studies that answered this question.				
Cancer Prostate in Sweden (CAPS) Hedelin, 2006[84] (Included in Simon MA[77])	Swedish men age 35–79	Case control study 261-item validated FFQ	National Prostate Cancer Registry	1,130 controls, 1,499 cases Dietary marine n-3s from fatty fish associated with decreased risk PC (OR for fatty fish ≥1/week vs. never 0.57 CI 0.43, 0.76; OR highest vs. lowest quartile marine FA 0.70, CI 0.51, 0.97) Significant interaction with small nuclear polymorphism in COX-2 gene (key enzyme in eicosanoid synthesis, over-expressed in PC tissue) but not with 4 other SNPs

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
KQ2 Key Question 2: Effects on Clinical Outcomes after Cancer Treatment **Key Question 2a: What is the evidence that omega-3 fatty acids alter the effects of cancer treatment on malignant tumors and clinical outcomes after cancer treatments?**				
Response to Chemotherapy **No studies in the original report assessed this outcome.**				
Bougneaux, 2009[23]	25 breast cancer patients with rapidly progressing visceral metastases that were not amenable to hormonal therapy or alternative treatment and without earlier chemotherapy for metastases Exclusion: history of any other cancer (with the exception of non-melanoma skin cancer or cervical carcinoma in situ), bilateral (without other metastatic location) or inflammatory breast cancer.	Phase II trial (open label single arm) testing effect of DHA on response of metastatic BC patients to chemotherapy (1.8g/d DHA of algal origin given as 9 capsules (3at each meal)(DHA is thought to sensitize cancer cells to chemo) DHA was administered from inclusion before initiation of chemotherapy (a 7–10-day loading period) and then for the 5 months of chemotherapy. Patients were asked to avoid antioxidant supplements	Primary outcome: Assessment of tumor response rate (clinically and radiographically), AE assessment Secondary outcome: time to progression (TTP) and overall survival (OS) Incorporation into plasma was also measured	Objective response rate was 44%. With a mean follow-up time of 31 months (range 2–96 months), the median TTP was 6 months. Median OS was 22 months and reached 34 months in the sub-population of patients (n=12) with the highest plasma DHA incorporation. The most common grade 3 or 4 toxicity was neutropaenia (80%). Conclusion: DHA improved outcome of chemotherapy for metastatic breast cancer
Sydney AUS 2 hospitals Read, 2007[22]	23 Colorectal cancer patients receiving chemotherapy (5 FU, irinotecan, folinic acid) with one prior cycle of chemo	Phase II trial testing effect of EPA-containing supplement 480ml/d for 3wks before resuming 3 3-wk cycles chemo	BW, body comp, CRP, QOL, dietary intake, PPL, and cytokines	20 patients completed 3 weeks and 15 completed 9 weeks. BW increased, LBM was maintained. Although protein and E intake decreased, perceived energy levels increased. CRP increased but returned to baseline levels by end of 9 weeks. Conclusion: EPA may help maintain nutritional status and QOL but RCTs needed

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Response to Surgery **Original report assessed Post-op complications, length of stay, mortality, nutritional parameters (nitrogen intake, calorie intake, albumin, transferrin, prealbumin), and Weight after surgery for upper GI malignancy resection** ***Post-operative complications* assessed in 14 studies (3 studies of n-3s alone and 11 studies of n-3s + arginine):** **Pooled random effects estimate for 3 studies of n-3s alone: 1.19 (0.66, 2.13)** **Pooled random effects estimate for n-3s + arg: 0.51 (0.40, 0.64)** **Pooled random effects estimate for all 14 studies: 0.57 (0.46, 0.71)** ***Length of Stay* (LOS) assessed in 13 studies (3 for n-3s alone and 10 for n-3s + arg):** **Pooled random effects estimate of LOS difference for 3 studies of n-3s alone: 1.09 days (-3.63, 5.81)** **Pooled random effects estimate for n-3s + arg: -3.33 days (-4.29, -2.38))** **Pooled random effects estimate for all 13 studies: -3.17 (-4.11, -2.26)** ***Mortality* assessed in 10 studies (4 for n-3s alone and 6 for n-3+arg)** **Pooled random effects estimate for 4 studies of n-3s alone: 1.42 (0.63, 3.38)** **Pooled random effects estimate for n-3s + arg: 1.01 (0.31, 3.35)** **Pooled random effects estimate for all 14 studies: 1.25 (0.64, 2.48)** **Nutritional parameters: 11 studies assessed effects of n-3s alone or in combination with arg and RNA on various nutrition metrics** **Of 6 studies, no significant effect seen on caloric intake; 1 study found an increase in N intake, and 1 found no effect; of 6 studies that assessed serum albumin and 3 that assessed transferrin, no effects were found; 2 of 6 studies that assessed prealbumin found significant increases in treated groups. Of 3 studies that assessed weight (loss), 1 showed less weight loss, one showed no difference, and one showed greater weight loss with n-3s.**				
Trinity College Hospital, Ireland Ryan, 2009[19]	53 esophagectomy patients	RCT cf EN (25 pts) with EN enriched with 2.2g EPA/d (28 pts) for 5d preop (oral) and 21d post-op (jejunal)	Esophageal/Bioimpedance, post-op complications, acutephase response, coagulation markers, serum cytokines	EPA significantly increased peripheral blood mononucleocyte (PBMC) EPA levels but did not affect incidence of major post-op complications. EPA improved retention of FFM (leg, arm, trunk) cf EN grp and attenuated stress response for TNF- α, IL-1-, IL-8
Okamoto, 2009[18]	82 consecutive patients who underwent surgery for gastric carcinoma, of whom 60 met the inclusion criteria: Exclusion: unresectable neoplasm, pervious abdominal radiotherapy,	RCT cf. IMPACT (arg+RNA+n-3s) and isocaloric conventional formula (MEDIF) preop for 7 days; same post-op diet	**Post-op complications:** wound infection, resp tract infection, intra-abdominal bleeding, anastomotic stenosis, cardiac dysfunction, systemic inflammatory response syndrome (SIRS);	Post-op infection rate and Req for post-op antibiotics sign decreased in IMPACT patients (7% vs. 28% and 3/30 vs. 10/30, respectively) SIRS duration significantly shorter in IMPACT group

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Okamoto, 2009[18] (cont.)	post-op chemotherapy; pulmonary, CV, hepatic, or renal disease; HX recent immunosuppressive therapy or immunological disease; ongoing infection; emergency operation; preoperative evidence of widespread metastatic disease or stenotic lesions		immune parameters; body weight, Hgb, prealbumin, albumin, transferrin, RBP, total cholesterol, triglyceride, cholinesterase, Cu, Zn	Length of hospital stay and weight loss did not differ between groups
5 Beijing hospitals Jiang, 2009[15]	206 patients with GI (60) or colon cancer (64) or other cancer (79), ages 18-70, undergoing surgery (final n=203) Exclusion:DM, abnormal lipid metabolism, renal dysfunction, liver dysfn, splenectomy, body temp>37.5C, concurrent hormone therapy, pregnancy	RCT of parenteral nutrition supplemented with Intralipid (soybean oil, giving a n-3/n-6 ratio of 1:7) vs. fish oil (n-3/n-6 1:3), isonitrogenous, isocaloric; 20-24h/d; 8 days post-op	No. post-op infections, occurrence of SIRS (systemic inflammatory response syndrome) during d1-7; length of hospital stay, costs	Fish oil associated with significantly fewer infectious complications on post-op d. 8: 12 vs. 4 Fish oil significantly decreased incidence of SIRS from 13/103 in the control group to 4/100 in the treated group.(p=0.039) Fish oil significantly decreased mean length of hospital stay from 17 to 15 days (p=0.041) Median weight loss in fish oil group was 1 kg (vs. 1.5 kg in controls) No serious adverse events: 1 instance of polyhydrosis and flushing in a control; small variations in body temp, respiratory rate, pulse, BP, liver and renal fn, blood lipids and glucose comparable in both groups

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample[#](n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Liang 2008[21]	42 patients undergoing radical colorectal resection for CRC w/indication for post-op TPN	RCT total parenteral nutrition supplemented with either soybean oil (LCT; Intralipid, Fresenius-Kabi, SO group, n = 21) or a combination of omega-3 fish oil and soybean oil (LCT:fish oil = 5:1, fish oil; Omegaven, Fresenius-Kabi, FO group, n = 21), up to a total of 1.2 g lipid/kg per day for 7 d postoperatively. Placebo and active tx were isocaloric and isonitrogenous	Routine blood test, biochemistry, systemic IL-6 and TNF-α; percentage of CD3+, CD4+, and CD8+ Lymphocytes: preop, post-op d 1 and 8. Patient outcome included mortality during the hospital stay, length of post-op hospital stay, and infectious complications	FO modulated immune response and lowered inflammatory response but no statistical difference in actual infectious complication rate. LOS non-significantly shorter in FO group (17.45 ± 4.80 d vs. 19.62 ± 5.59 d, P = 0.19). No statistically significant difference in mortality (no deaths in either group)
DeLuis, 2008[14]	73 ambulatory postsurgical patients with oral and laryngeal cancer (without recent weight loss) Exclusion: severe renal and hepatic dysfunction, ongoing infection, fever in preceding month , major GI disease, autoimmune disorder, steroid treatment, and medication that could modulate weight or metabolism	RCT Randomization to two cans/day of n-3fatty acid (EPA+DHA)-enhanced (Grp 1 n-3/n-6=3.7 or n-6/n-3=0.27) vs. Grp. 2 (n-3/n-6=0.99 or n6/n3=1.01)	Oral and laryngeal cancer/ Ascertainment?/ BW, body mass, post-op complications, prealbumin, albumin, transferring, lymphocytes Ascertained adherence via measurement and diaries	Duration of supplementation 85.8±26 vs. 88.9± 22.6. Post-op infectious complications were non-significantly higher in group 1. No difference between groups in any nutritional parameter; all were higher than baseline levels.
Japanese hospital Sakurai, 2007[20] IMPACT IEEF (article does not state that formula contains n-3s)	30 patients with esophageal carcinoma who underwent radical esophagectomy jejunostomy	RCT cf Ajinomoto IMPACT IEEF to regular polymeric enteral formula perioperatively (3 days preop, 1000 cal/d) and post-op approx 14d, 250 cal/d increasing progressively)	Esophageal Ascertainment unclear Pre- and post-op serum total protein, serum albumin, peripheral white blood cell count, % lymphocyte fraction, total lymphocyte count, IGF-1, thransthyretin, transferrin**,** retinol binding protein, serum DHLA, DHA, EPA, AA, various immunological parameters, post-op complications, hospital stay	No differences were seen in SIRS, resumption of normal feeding, post-op LOS, or post-op complications; IMPACT increased total lymphocyte count at 3 and 5 d post-op and a shift toward B cell proliferation.

Table C2. Effects of omega-3s on cancer risk and response to treatment (continued)

Cohort* or Trial/First Author/Year	Sample#(n)/Inclusion Criteria/Exclusion Criteria	Study Design/Intervention or Independent Variable/Duration	Type of Cancer/ Ascertainment/Outcome(s) Assessed	Findings
Lobo, 2006[16]	120 patients undergoing resection for upper GI cancers, 30-80 yrs Exclusion: metastatic or unresectable disease, pregnancy, use of immunosuppressives	RCT Jejunostomy feeding (PN) with Stresson (n6/n3=3.45:1+arginine 9g/1250 cal) or Nutrison high protein (n6/n3=5:1+arg 3g/1250 cal)	Cancer of the pancreas, esophagus, stomach/ Post-op complications, non-infectious complications, mortality, duration of hospital stay, albumin, CRP, Hgb, white cell ct	No significant differences between groups in infectious post-op complications, albumin, CRP, white cell count, Hgb Short and long term survival (mortality) were the same: 6 deaths in each group
Japanese Hospital Aiko, 2005[90]	28 Patients w/ esophageal carcinoma who underwent surgery Exclusion: presurgical chemo or radiotherapy, ligated or resected thoracic duct, longerm fasing, Type 1 DM, renal or hepatic failure, previous use of corticosteroids or other immunosuppressants,	RCT Randomization to post-op enteral feeding with standard formula (Ensure w/ n-6 to n-3 ratio of 44, EN) or similar formula supplemented with oils to give a n-6 to n-3 ratio of 3 (RAC). All pts received parenteral mixture also.	Esophageal/ Ascertainment? Markers of coagulation and fibrinolysis, concn IL-6, 8; 6-keto-PGF-1α	Compared to EN (low n-3), RAC (higher n-3) decreased inflammation, including attenuating the normal post-op decrease in platelet count, platelet aggregation, coagulation activity, and cytokine production
DeLuis, 2005[17]	65 ambulatory post surgical patients with oral and laryngeal cancer and recent weight loss Exclusion: severe renal and hepatic dysfunction, ongoing infection, fever in preceding month , major GI disease, autoimmune disorder, steroid treatment, and medication that could modulate weight or metabolism	RCT of supplements: Grp 1 received n-6/n-3= 0.27(n-3/n-6=3.7/1), no supplemental arg vs. Grp. 2: n-6/n-3=0.92 (n-3/n-6=1.09) + arg	See DeLuis 2008	Post-op infectious complications and weight stabilization were similar in both groups. No difference between groups in any other parameter; all were higher than baseline levels.
Snyderman, 1999[91]	136 patients with stage II-IV squamous cell carcinoma of the oral cavity, larynx, pharynx undergoing surgery to cure and in need of post-op supplementation	RCT of IMPACT cf. standard formula for at least 7 days	Change in BW, lab evaluations of nutritional status, infectious and wound healing complications, duration of hospitalization	IMPACT was associated with a significant decrease in post-op infectious complications; no significant difference in wound healing, LOS. Serum albumin was higher in IMPACT recipients Confirms earlier findings

*Trial name if named trial
#Gender, age (number)

Cardiovascular Risk Factors

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#
Original Key Questions (abbreviated and rephrased) *What is the effect of omega-3 fatty acids (EPA, DHA, ALA; fish; supplements or dietary) on cardiovascular risk factors and intermediate markers of cardiovascular disease (see list of outcomes below)?* *How do the effects differ by* ● *Dose* ● *Duration of intake* ● *Specific omega-3 fatty acid (or their ratios)* ● *Source (e.g., dietary fish, dietary oils, dietary plants, fish oil supplement, flax seed supplement)* ● *Ratio of omega-6 to omega-3 fatty acids* ● *Population (men, premenopausal women, postmenopausal women, different age groups)* ● *Baseline dietary intake of omega-3 fatty acids* ● *Presence of potential confounders* ○ *Body mass index* ○ *Blood pressure* ○ *Medications* ● *Pre-existing conditions* ○ *Diabetes* ○ *Hypertension* ○ *Hyperlipidemia* ○ *Known cardiovascular disease* *Are the effects sustained after the intervention or exposure stops?*					

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#
					Net effect
Total cholesterol (TC) 23 RCTs (20 FO, 4 ALA) (N≥60 [parallel design], N≥40 [crossover]) 1. The studies "were heterogeneous, but mostly found small (0% to 6%), nonsignificant net increases in level of [total cholesterol]." 2. "The effect of plant oils (ALA) on [TC] was possibly weaker but similar to the effect of marine oils." 3. 19 fish oil (FO) studies: Summary net effect **0 (95% CI -1, +2) mg/dL [μ=0.4257; SE=0.9537]**; Higher mean baseline TC associated with larger net decrease in TC.[1] 4. 5 ALA studies: Range of net effects -1, +13 mg/dL[2] 5. No clear evidence of different effects in different populations 6. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of n-3 FA 7. No difference in effect seen across 5 weeks and 2 years of exposure. 8. No evidence on sustainment of effect.	Pan, 2009[92]	Meta-analysis (flaxseed)	1548	Non-sig. decrease in TC. Note: this includes lignans (0g ALA) intervention for 181 patients.	-0.10 mmol/L (-0.20, 0.00)
			Varies	Meta-regression analysis showed that sex, type of intervention (whole flaxseed, flaxseed oil, or lignan supplement (0g ALA)), study quality (Jadad score), and initial lipid concentrations influenced the net change in TC.	-0.19 (-0.29, -0.09) Whole flaxseed studies
					+0.06 (-0.07, 0.19) Flaxseed oil studies
					-0.24 (-0.36, -0.12) Female studies
					+0.09 (-0.05, 0.23) Male studies
	Oikawa, 2009[26] (JELIS)	RCT (EPA supplement)	14,080	Among those with normoglycemia, sig lower final TC with EPA (not clinically relevant)	Estimated: -2 (-2.9, -1.1) [SE 0.46] **-1.5 (-2.4, -0.7)**
			4565	Among those with impaired glucose metabolism, sig lower final TC with EPA (not clinically relevant)	Estimated: -1 (-2.8, 0.8) [SE 0.90] **-1.4 (-2.2, -0.7)**
	Saitio, 2008[93] (JELIS)		957	For high-risk group (TG ≥150 mg/dL and HDL-C <40 mg/dL), no sig effect on TC.	Estimated: +1 (-3.27, 5.27)
	Hjerkinn, 2005[94]	RCT: 2X2 factorial (Dietary counseling, 2.4g/d n-3 PUFA)	281	2.4 g/d n-3 in treatment group with no diet intervention in both groups produced a non-sig. reduction in TC.	-0.1 (-0.38, 0.18)
			280	2.4 g/d n-3 in treatment group with diet intervention in both groups produced a non-sig. reduction in TC.	-0.2 (-0.46, 0.06)

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#	
	Caslake, 2008[95] (FINGEN)	Randomized, dose-response, cross-over (FO supplement 0.7 or 1.8 g EPA+DHA/d)	312	Both 0.7 and 1.8 g FO dose groups had no sig. effect on TC, and there was no sig. dose effect.	Net diff cannot be estimated because the SE for all 3 groups was the same due to crossover design	
	Grundt, 2003[96]	RCT (FO supplement ~2g EPA+DHA/d)	246	No sig. effect on TC	Estimated: -0.24 (-0.54, 0.06) mmol/L	
	Griffin, 2006[97] (OPTILIP)	RCT (6%of kcal from PUFAs with an n6:n3 of 10:1 (control), 5:1 when the n3 fatty acids were predominantly α-linolenic acid (18:3n3), 3:1 when the n3 fatty acids were predominantly long-chain n3 PUFAs (EPA and DHA), or both α-linolenic acid and long chain n3 PUFA)	258	No sig. effect on TC	Estimated: n3 LC PUFA: 0.16 (-0.21, 0.53) High α-linolenic acid: 0 (-0.39, 0.39) N3 LC PUFA + α-linolenic acid: 0.07 (-0.32, 0.46) Moderate α-linolenic acid: 0.13 (-0.26, 0.52) (in mmol/L)	
	Cazzola, 2007[98]	RCT (Placebo, 1.35, 2.7, or 4.05 g EPA/day in young (18-42y) and older (53-70) males)	155 total	No significant effects of treatment on the plasma concentrations of TC were observed. At right, net change is given (young left, older right) vs. placebo. Each row is increasing dose of EPA.	0 (-0.44, 0.44)	0 (-0.39, 0.39)
					-0.10 (-0.49, 0.29)	0.10 (-0.29, 0.49)
					0 (-0.39, 0.39)	0.20 (-0.19, 0.59)
	Rallidis, 2004[99]	RCT (linseed oil)	90	Non-sig. increase in TC.	+10 (-9.5, 29.5)	
	Lovegrove, 2004[100]	RCT (4 g fish oil)	84	No change in TC (in Europeans and Indo-Asians)	Euro: +0.1 (-0.1, 0.3) mmol/L Indian: 0 (-0.4, 0.4)	

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#
	Lee, 2006[101]	RCT (*Omacor* (a pharmaceutical capsule formulation of highly purified and concentrated n_3 PUFAs; Solvay Healthcare, Southampton, UK) 1g/day)	77	Non-sig decrease in TC.	-0.02 (-0.37, 0.33)
	Rallidis, 2003[102]	RCT (linseed oil)	76	Non-sig. increase in TC.	+10 (-10.17, 30.17)
	Hill, 2007[103]	RCT 2X2 Factorial (6g tuna oil, exercise)	38	6g tuna oil with no exercise intervention in both groups produced non-sig. reduction in TC.	-0.01 (-0.77, 0.75)
			37	6g tuna oil with exercise in both groups produced non-sig increase in TC.	+0.06 (-0.74, 0.86)
	Mita, 2007[104]	RCT (1800 EPA mg/d)	60	Non-sig reduction in TC.	-0.12 (-0.58, 0.34)
					Net effect
LDL cholesterol 15 RCTs (14 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 9. "The effect of omega-3 fatty acid consumption was fairly uniform across studies. Most found a net increase in LDL with treatment." 10. "The effect of plant oils (ALA) on [LDL] was possibly weaker but similar to the effect of marine oils."	Pan, 2009[92]	Meta-analysis (flaxseed)	1471	Sig. decrease in LDL. Note: this includes lignans (0g ALA) intervention for 181 patients.	-0.08 (-0.16, 0.00)
			Varies	Meta-regression analysis showed that sex, type of intervention (whole flaxseed, flaxseed oil, or lignan supplement (0g ALA)), study quality (Jadad score), and initial lipid concentrations influenced the net change in LDL.	-0.16 (-0.25, -0.06) Whole flaxseed studies
					+0.06 (-0.04, 0.17) Flaxseed oil studies
					-0.17 (-0.28, -0.06) Female studies
					+0.07 (-0.04, 0.18) Male studies

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#	
11. 13 fish oil studies: Summary net effect **+6 (95% CI +3, +8) mg/dL**[3] 12. 3 ALA studies: Range of net effects -2, +3 mg/dL[4] 13. No clear evidence of different effects in different populations 14. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of n-3 FA 15. No difference in effect seen across 8 weeks and 2 years of exposure. 16. No evidence on sustainment of effect.	Oikawa, 2009[26] (JELIS)	RCT (EPA supplement)	14,080	Among those with normoglycemia, no significant effect	Estimated: -1 (-2.0, -0.04) [SE 0.49] **-0.2 (-1.1, +0.7)**	
			4565	Among those with impaired glucose metabolism, no significant effect	Estimated: +1 (-0.8, +2.7) [SE 0.88] **+0.1 (-0.7, +0.9)**	
	Saitio, 2008[93] (JELIS)		957	For high-risk group (TG ≥150 mg/dL and HDL-C <40 mg/dL), no sig effect on LDL.	Estimated: 0 (-4.13, +4.13)	
	Caslake, 2008[95] (FINGEN) 18779276	Randomized, dose-response, cross-over (FO supplement 0.7 or 1.8 g EPA+DHA/d)	312	Both 0.7 and 1.8 g FO dose groups had sig. higher LDL (P=0.01), and there was no sig. dose effect.	Net diff cannot be estimated because the SE for all 3 groups was the same due to crossover design	
	Griffin, 2006[97] (OPTILIP)	RCT (6%of kcal from PUFAs with an n6:n3 of 10:1 (control), 5:1 when the n3 fatty acids were predominantly α-linolenic acid (18:3n3), 3:1 when the n3 fatty acids were predominantly long-chain n3 PUFAs (EPA and DHA), or both α-linolenic acid and long chain n3 PUFA)	258	No sig. effect on LDL	Estimated: n3 LC PUFA: 0.08 (-0.29, 0.45) High α-linolenic acid: -0.05 (-0.43, 0.33) N3 LC PUFA + α-linolenic acid: 0.2 (-0.19, 0.59) Moderate α-linolenic acid: 0.04 (-0.35, 0.43) (in mmol/L)	
	Maki, 2010[105]	RCT (n-3 4g/d or placebo combined with open-label simvastatin 40 mg/d)	256	Subgroup analysis: the baseline LDL cholesterol had a significant interaction with n-3 treatment for the LDL cholesterol response (p=0.022 for the treatment by baseline tertile interaction)	% change from baseline Tertile 1 (LDL <80.4 mg/dl): n-3 9.5% vs. placebo 1.1% Tertile 2 (80.4-<99.0mg/dl): n-3 -0.9% vs. placebo -3.8% Tertile 2 (≥99.0mg/dl): n-3 -6.4% vs. placebo -4.5%	
	Cazzola, 2007[98]	RCT (Placebo, 1.35, 2.7, or 4.05 g EPA/day	155 total	No significant effects of treatment on the plasma concentrations of LDL were	0.30 (-0.09, 0.69)	-0.10 (-0.49, 0.29)
					0.10 (-0.18, 0.38)	-0.10 (-0.49, 0.29)

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#	
		in young (18-42y) and older (53-70) males)		observed. At right, net change is given (young left, older right) vs. placebo. Each row is increasing dose of EPA.	0.20 (-0.19, 0.59)	0.10 (-0.18, 0.38)
	Tuttle, 2008[106]	RCT (Med. Diet (>.75% cal. omega-3) vs. low-fat diet in MI survivors)	101	Non-sig. increase in LDL.	+3 (-8.7, 14.7)	
	Rallidis, 2004[99]	RCT (linseed oil vs. safflower oil)	90	Non-sig. increase in LDL.	+3 (-15.9, 21.9)	
	Lovegrove, 2004[100]	RCT (4 g fish oil)	84	No change in LDL (in Europeans and Indo-Asians)	Euro: +0.1 (-0.1, 0.3) mmol/L Indian: +0.1 (-0.3, 0.5)	
	Lee, 2006[101]	RCT (*Omacor* (a pharmaceutical capsule formulation of highly purified and concentrated n_3 PUFAs; Solvay Healthcare, Southampton, UK) 1g/day)	77	Non-sig. decrease in LDL vs. control.	-0.05 (-0.37, 0.27)	
	Rallidis, 2003[102]	RCT (linseed oil vs. safflower oil)	76	Non-sig increase in LDL	+3 (-16.55, 22.55)	
					Net effect	
HDL cholesterol 19 RCTs (18 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 17. The studies "were heterogeneous, but mostly found small (0% to 6%), non-significant net increases in level of [HDL]."	Pan, 2009[92] 19515737	Meta-analysis (flaxseed)	1353	Non-sig. decrease in HDL. Note: this includes lignans (0g ALA) intervention for 181 patients.	-0.02 (-.04, 0.00)	
	Oikawa, 2009[26] (JELIS)	RCT (EPA supplement)	14,080	Among those with normoglycemia, no significant effect	Estimated: -1 (-1.5, -0.5) [SE 0.28] **-0.2 (-0.6, +0.3)**	
			4565	Among those with impaired glucose metabolism, sig lower final HDL with EPA (not clinically relevant)	Estimated: 0 (-0.9, +0.9) [SE 0.46] **-0.1 (-0.5, +0.3)**	

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#
18. "The effect of plant oils (ALA) on [HDL] was possibly weaker but similar to the effect of marine oils." 19. 17 fish oil studies: Summary net effect **+1.6 (95% CI +0.8, +2.3) mg/dL**[5] 20. 3 ALA studies: Range of net effects -1, +1 mg/dL[6] 21. No clear evidence of different effects in different populations 22. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of n-3 FA 23. " No clear effect across [or within 5] studies… based on duration of intervention or exposure." 24. No evidence on sustainment of effect.	Saitio, 2008[93] (JELIS)		957	For high-risk group (TG ≥150 mg/dL and HDL-C <40 mg/dL), no sig effect on HDL.	Estimated: 0 (-0.99, +0.99)
	Hjerkinn, 2005[94]	RCT: 2X2 factorial (Dietary counseling, 2.4g/d n-3 PUFA)	281	2.4 g/d n-3 in treatment group with no diet intervention in both groups produced a non-sig. increase in HDL.	+0.07 (-0.02, 0.16)
			280	2.4 g/d n-3 in treatment group with diet intervention in both groups produced a non-sig. increase in HDL.	+0.02 (-0.08, 0.12)
	Caslake, 2008[95] (FINGEN)	Randomized, dose-response, cross-over (FO supplement 0.7 or 1.8 g EPA+DHA/d)	312	Both 0.7 and 1.8 g FO dose groups had sig. higher HDL (P<0.01), and there was no sig. dose effect.	Net diff cannot be estimated because the SE for all 3 groups was the same due to crossover design
	Grundt, 2003[96]	RCT (FO supplement ~2g EPA+DHA/d)	239	EPA+DHA supplement sig. increased HDL (P<0.001)	Estimated: 0.13 (0.05, 0.21) mmol/L
	Griffin, 2006[97] (OPTILIP)	RCT (6%of kcal from PUFAs with an n6:n3 of 10:1 (control), 5:1 when the n3 fatty acids were predominantly α-linolenic acid (18:3n3), 3:1 when the n3 fatty acids were predominantly long-chain n3 PUFAs (EPA and DHA), or both α-linolenic acid and long chain n3 PUFA)	258	No sig. effect on HDL	Estimated: n3 LC PUFA: 0.01 (-0.15, 0.17) High α-linolenic acid: -0.01 (-0.18, 0.16) N3 LC PUFA + α-linolenic acid: 0.03 (-0.15, 0.21) Moderate α-linolenic acid: -0.01 (-0.18, 0.16) (in mmol/L)

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#	
	Maki, 2010[105]	RCT (n-3 4g/d or placebo combined with open-label simvastatin 40 mg/d)	256	Subgroup analysis: the baseline LDL cholesterol did not have a significant interaction with n-3 treatment for the HDL cholesterol.	% change from baseline Tertile 1 (LDL <80.4 mg/dl): n-3 4% vs. placebo -1% Tertile 2 (80.4-<99.0mg/dl): n-3 2% vs. placebo -1% Tertile 2 (≥99.0mg/dl): n-3 4% vs. placebo -1%	
	Cazzola, 2007[98]	RCT (Placebo, 1.35, 2.7, or 4.05 g EPA/day in young (18-42y) and older (53-70) males)	155 total	No significant effects of treatment on the plasma concentrations of HDL were observed. At right, net change is given (young left, older right) vs. placebo. Each row is increasing dose of EPA.	-0.10 (-0.38, 0.18)	0 (-0.28, 0.28)
					-0.10 (-0.38, 0.18)	0.20 (-0.08, 0.48)
					0 (-0.39, 0.39)	0 (-0.28, 0.28)
	Tuttle, 2008[106]	RCT (Med. Diet (>.75% cal. omega-3) vs. low-fat diet in MI survivors)	101	Non-sig. decrease in HDL.	-2 (-6.2, 2.2)	
	Rallidis, 2004[99]	RCT (linseed oil vs. safflower oil)	90	Non-sig. decrease in HDL.	-.8 (-4.8, 3.1) mg/dl	
	Lovegrove, 2004[100]	RCT (4 g fish oil)	84	Significant (relative) increase in HDL (in Europeans and Indo-Asians, combined, P=0.03)	Euro: +0.1 (-0.02, 0.2) mmol/L Indian: 0 (-0.2, 0.2)	
	Lee, 2006[101]	RCT (*Omacor* (a pharmaceutical capsule formulation of highly purified and concentrated n_3 PUFAs; Solvay Healthcare, Southampton, UK) 1g/day)	77	Non-sig. effect on HDL vs. control.	+0.01 (-0.11, 0.13)	
	Rallidis, 2003[102]	RCT (linseed oil vs. safflower oil)	76	Non-sig. decrease in HDL	-0.8 (-4.92, 3.32)	

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#
	Hill, 2007[101]	RCT 2X2 Factorial (6g tuna oil, exercise)	38	6g tuna oil with no exercise intervention in both groups produced non-sig. increase in HDL.	+0.1 (-0.23, 0.43)
			37	6g tuna oil with exercise in both groups produced non-sig increase in HDL.	+0.15 (-0.16, 0.46)
	Mita, 2007[104]	RCT (1800 EPA mg/d)	60	Non-sig. increase in HDL	+0.12 (-0.12, 0.36)
					Net effect
Triglycerides 19 RCTs (18 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 25. "Most of [the] studies reported a net decrease in Tg of about 10% to 33%." "However, 1 of 2 studies of plant oils (ALA) found a net increase in TG." 26. 17 fish oil studies: Summary net effect **-27 (95% CI -33, -20) mg/dL**; Higher baseline TG and higher dose associated with larger effect.[7] 27. 3 ALA studies: Range of net effects -19, +23 mg/dL[8] 28. "The effect was… generally consistent among healthy subjects and patients with CVD, dyslipidemia, or at elevated risk of CVD." (No study of diabetic patients had sufficient number of subjects to be analyzed.)	Pan, 2009[92]	Meta-analysis (flaxseed)	1359	Non-sig. decrease in Triglycerides. Note: this includes lignans (0g ALA) intervention for 181 patients.	-0.03 (-0.08, 0.02)
	Oikawa, 2009[26] (JELIS)	RCT (EPA supplement)	14,080	Among those with normoglycemia, sig lower final TG with EPA (not clinically relevant)	Estimated from medians and IQR: -8 (-10, -6) [SE 1.2] **-10 (-12, -8)**
			4565	Among those with impaired glucose metabolism, sig lower final TG with EPA (not clinically relevant)	Estimated from medians and IQR: -12 (-17, -7) [SE 2.6] **-10 (-12, -8)**
	Saitio, 2008[93] (JELIS)		957	For high-risk group (TG ≥150 mg/dL and HDL-C <40 mg/dL), sig decreased in TG	EPA: -23% (nd) Control: -18% (nd) P=0.012 **(not included in MA)**
	Hjerkinn, 2005[94]	RCT: 2X2 factorial (Dietary counseling, 2.4g/d n-3 PUFA)	281	2.4 g/d n-3 in treatment group with no diet intervention in both groups produced a non-sig. decrease in TG.	-0.17 (-0.38, 0.04) **-10.2 (-12.2, -8.3)**
			280	2.4 g/d n-3 in treatment group with diet intervention in both groups produced a sig. decrease in TG.	-0.23 (-0.42, -0.04) **-10.4 (-12.3, -8.4)**

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#
29. "The effect was dose-dependent… [and] greater in studies with higher mean baseline TG." 30. "Limited data suggest the effect is not related to sex, age, weight, background diet, or lipid treatment." 31. "The effect of duration of intervention is unclear." 32. No evidence on sustainment of effect.	Caslake, 2008[95] (FINGEN)	Randomized, dose-response, cross-over (FO supplement 0.7 or 1.8 g EPA+DHA/d)	312	Both 0.7 and 1.8 g FO dose groups had sig. reduced TG (-8% and -11.2%, respectively, P<0.001), and there was no sig. dose effect.	Net diff cannot be estimated because the SE for all 3 groups was the same due to crossover design
			149	In men, there was sig. dose effect on TG reduction	Data were not reported.
			163	In women, there was no sig. dose effect on TG reduction	Data were not reported. P<0.038 for treatment x sex interaction.
	Grundt, 2003[96]	RCT (FO supplement ~2g EPA+DHA/d)	145	EPA+DHA supplement sig. lowered HDL (P<0.001)	Estimated: -0.62 (-0.83, -0.41) mmol/L **-10.9 (-12.8, -8.9)**
	Griffin, 2006[97] (OPTILIP)	RCT (6%of kcal from PUFAs with an n6:n3 of 10:1 (control), 5:1 when the n3 fatty acids were predominantly α-linolenic acid (18:3n3), 3:1 when the n3 fatty acids were predominantly long-chain n3 PUFAs (EPA and DHA), or both α-linolenic acid and long chain n3 PUFA)	258	No sig. effect on TG	Estimated: n3 LC PUFA: 0.02 (-0.19, 0.23) **-10.7 (-12.7, -8.8)** High α-linolenic acid: 0.01 (-0.22, 0.24) **(not included in MA)** N3 LC PUFA + α-linolenic acid: -0.13 (-0.34, 0.08) **(not included in MA)** Moderate α-linolenic acid: 0.13 (-0.10, 0.34) (in mmol/L) **(not included in MA)**
	Maki, 2010[105]	RCT (n-3 4g/d or placebo combined with open-label simvastatin 40 mg/d)	256	Subgroup analysis: the baseline LDL cholesterol did not have a significant interaction with n-3 treatment for TG.	% change from baseline Tertile 1 (LDL <80.4 mg/dl): n-3 -27% vs. placebo -8% Tertile 2 (80.4-<99.0 mg/dl): n-3 -32% vs. placebo -5% Tertile 2 (≥99.0mg/dl): n-3 -30% vs. placebo -6% **(not included in MA)**

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#		
	Lindman, 2004[107]	RCT (2*2 factorial designed study, corn oil 2.4g/d; corn oil 2.4g/d + dietary advice; n-3 supplements 2.4g/d; n-3 supplements 2.4g/d + dietary advice)	219	N-3 supplementation significantly reduced the TG levels compared to no n-3 supplementation group.	ß (95% CI) TG (mmol/l): -0.11 (-0.19, -0.03) (p=0.01) **-10.6 (-12.5, -8.8)**		
	Cazzola, 2007[98]	RCT (Placebo, 1.35, 2.7, or 4.05 g EPA/day in young (18-42y) and older (53-70) males)	155 total	There was a sig. decrease in TG for the young groups across all dosages. Non-sig. effect for the older groups. At right, net change is given (young left, older right) vs. placebo. Each row is increasing dose of EPA.		Young	Old
					Low dose	-0.40 (-0.68, -0.12) **-10.8 (-12.7, -8.9)**	0 (-0.28, 0.28) **-10.7 (-12.6, -8.9)**
					Medium dose	-0.40 (-0.68, -0.12) **-10.9 (-12.7, -9.0)**	-0.10 (-0.38, 0.18) **-10.9 (-12.7, -9.0)**
					High dose	-0.30 (-0.58, -0.02) **-10.9 (-12.8, -9.1)**	-0.10 (-0.38, 0.18) **-10.9 (-12.8, -9.1)**
	Tuttle, 2008[106]	RCT (Med. Diet (>.75% cal. omega-3) vs. low-fat diet in MI survivors)	101	Non-sig. increase in TG.	+41 (-10.4, 92.4) **-10.9 (-12.7, -9.0)**		
	Lovegrove, 2004[100]	RCT (4 g fish oil)	84	Significant decrease in TG (in Europeans and Indo-Asians, combined, P=0.002)	Euro: -0.1 (-0.3, 0.1) mmol/L **-10.8 (-12.7, -9.0)** Indian: -0.5 (-0.9, -0.1) **-10.9 (-12.7, -9.1)**		

Table C3. Effects of omega-3 fatty acids on cardiovascular risk factors – new study data (continued)

Report Findings/Conclusions*	Article	Design (interv)	N	Study Findings	Data#
	Lee, 2006[101]	RCT (*Omacor* (a pharmaceutical capsule formulation of highly purified and concentrated n_3 PUFAs; Solvay Healthcare, Southampton, UK) 1g/day)	77	No sig. effect on TG.	0 (-0.36, 0.36) **-10.9 (-12.7, -9.1)**
	Rallidis, 2003[102]	RCT (linseed oil vs. safflower oil)	76	Non-sig. increase in TG	+25 (-20.89, 70.89) **(not included in MA, because this study examined ALA)**
	Hill, 2007[103] 17490962	RCT 2X2 Factorial (6g tuna oil, exercise)	38	6g tuna oil with no exercise intervention in both groups produced non-sig. decrease in TG.	-0.21 (-0.71, 0.29) **-10.9 (-12.7, -9.1)**
			37	6g tuna oil with exercise in both groups produced non-sig decrease in TG.	-0.31 (-1.23, 0.61) **-10.9 (-12.7, -9.1)**
	Mita, 2007[104]	RCT (1800 EPA mg/d)	60	Non-sig. increase in TG.	+0.18 (-0.30, 0.66) **-10.9 (-12.7, -9.0)**

* In the first column (Report findings/conclusions), the data in bold text are the meta-analyses from the report (or ancillary journal articles) that we used as the base for the "Ottawa Method."

In the fifth column (Data), all values are net differences (of continuous outcomes) between omega-3 fatty acid and control; the units of measurement are not included. The values and 95 percent confidence intervals (the data in parentheses) in bold text are the FEM meta-analyses with the addition of that row's study. Estimates and 95 percent confidence intervals in gray highlighting are positive signals (B1 or B2 using the Ottawa method). These are the last meta-analyses done for the respective outcome.

Appendix D. Informational Letters

Cognitive Function

Figure D1. Informational letter for cognitive function

Updating Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases

Title: Effects on Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Disease

Conclusions From Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: What is the evidence that omega-3 FA play a role in maintaining cognitive function in normal aging?			
Only one study that met inclusion criteria assessed the role of omega-3 FA in maintaining cognitive function. Fish consumption was only weakly associated with a reduced risk of cognitive impairment and had no association with cognitive decline; omega-3 FA consumption was not associated with either outcome.	☐	New Evidence: _____ _____ _____	☐
Key Question 2: What is the evidence that omega-3 FA affect the incidence of dementia including Alzheimer's disease?			
Three studies evaluated the effect of omega-3 FA on the incidence of dementia. All three of the studies assessed the incidence of dementia relative to fish consumption; one also assessed risk relative to total omega-3 fatty consumption, and relative to each alpha-linolenic acid (ALA; 18:2n-3); eicosapentaenoic acid with a significant reduction in the incidence of non-Alzheimer's dementia in only one of the studies. Fish consumption was associated with a reduced risk of Alzheimer's dementia in all three of the studies but this association was significant in only one study. Total omega-3 FA consumption and consumption of DHA (but not ALA or EPA) were associated with a significant reduction in the incidence of Alzheimer's.	☐	New Evidence: _____ _____ _____	☐

Figure D1. Informational letter for cognitive function (continued)

Conclusions From Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 3: What is the evidence that omega-3 FA are effective in the treatment of dementia including Alzheimer's disease?			
Only one study assessed the effects of omega-3 FA for the treatment of dementia. DHA resulted in a small improvement in scores on a dementia rating scale.	☐	New Evidence: _____ _____ _____	☐
Key Question 4: What is the evidence that omega-3 FA affect the incidence of neurological diseases?			
Four studies addressed the association of omega-3 FA consumption with risk or incidence of particular neurological diseases other than dementia. Two studies that assessed the association between omega-3 FA intake and the incidence of multiple sclerosis found no significant effects, although one study found a reduced risk with fish consumption among women. The one study that assessed the association between omega-3 FA consumption and the risk for Parkinson's disease found no significant association for fish, ALA, EPA, or DHA. The one study that assessed the association between maternal omega-3 FA consumption and the risk of giving birth to a child with cerebral palsy found that consumption of fish once a week throughout pregnancy was association with a lower risk.	☐	New Evidence: _____ _____ _____	☐
Key Question 5: What is the evidence that omega-3 FA prevent the progression of multiple sclerosis?			
Three studies reported on the side effects of omega-3 FA intake on the progression of multiple		New Evidence:	

Figure D1. Informational letter for cognitive function (continued)

Conclusions From Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
sclerosis. In one study, treatment with an omega-3 FA supplement, MaxEPA, had no effect on disability or relapse rates. However, two other studies reported a significant reduction in disability and one reported improvement on an index of disease progression.	☐	_____ _____ _____	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

Cancer

Figure D2. Informational letter for cancer

Updating Omega-3 Fatty Acids on Cancer

Title: Effects of Omega-3 Fatty Acids on Cancer

Conclusions From Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: Effect of Tumor Incidence **1a: What is the evidence that omega-3 fatty acids reduce the incidence of tumors (in humans)? For what type of tumors?**			
Among 43 risk ratios calculated across 19 cohorts for 11 different types of cancer and 5 different ways to assess omega-3 fatty acid consumption (fish consumption, total omega-3 consumption, alpha-linolenic acid [ALA] consumption, docosahexaenoic acid [DHA] consumption, and eicosapentaenoic acid [EPA] consumption), only four are statistically significant. Significant associations between omega- 3 consumption and cancer risk were reported: • for lung cancer in two studies; • for breast cancer in one; • for prostate cancer in one; and • for skin cancer in one. However, for lung cancer, one of the significant associations was for increased cancer risk and the other was for decreased risk (four other risk ratios were not significant for lung cancer). For breast cancer, five other estimates did not show a significant association. Only one study assessed skin cancer risk. No effects were reported for cancers of the aerodigestive tract, bladder cancer, colorectal cancer, lymphoma, ovarian cancer, pancreatic cancer, or stomach cancer. Thus, omega-3 fatty acids do not appear to decrease overall cancer risk.	☐	New Evidence: _____ _____ _____	☐

Figure D2. Informational letter for cancer (continued)

Conclusions From Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Effect of Tumor Incidence **Key Question 1b: If omega-3 fatty acids influence the incidence of tumors, is there an inverse relationship with intake?**			
Data were insufficient to permit assessment of a dose-response relationship.	☐	New Evidence: _____ _____ _____	☐
Effect of Tumor Incidence **Key Question 1c: Is there a temporal relationship with intake?**			
Data were insufficient to permit assessment of a temporal relationship	☐	New Evidence: _____ _____ _____	☐
Effect of Tumor Incidence **Key Question 1d: If omega-3 fatty acids influence the incidence of tumors, what is the evidence that genes involved in omega-3 fatty acid transport or metabolism influence the magnitude or direction of the influence on tumor incidence?**			
No studies were identified that investigated the role of omega-3 fatty acid transport or metabolism genes in any putative effect of omega-3 fatty acids on tumor incidence	☐	New Evidence: _____ _____ _____	☐

Figure D2. Informational letter for cancer (continued)

Conclusions From Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Effect of Tumor Incidence **Key Question 1e: What is the evidence that the response to omega-3 fatty acids is independent of the intake of antioxidants such as vitamin E or other bioactive food components?**			
No studies were identified that allowed this question to be answered	☐	New Evidence: _____ _____ _____	☐
Effect of Tumor Incidence **Key Question 1f: What is the evidence that the response is modified by the state of the immune system?**			
No studies were identified that examined the possible modification of the effect of omega-3 fatty acids by immune status.	☐	New Evidence: _____ _____ _____	☐
Key Question 2: Effects on Clinical Outcomes after Cancer Treatment **Key Question 2a: What is the evidence that omega-3 fatty acids alter the effects of cancer treatment on malignant tumors and clinical outcomes after cancer treatments?**			
We identified 19 studies from which the effect of omega-3 fatty acids on clinical outcomes after cancer therapy could be ascertained, all of which pertained to patients who had undergone cancer surgery for upper gastrointestinal malignancies. We did not identify any studies that assessed the effects of omega-3 fatty acids on clinical outcomes after chemotherapy or radiation surgery. Among the identified studies, 14 described the effect on post-operative complications, 13 on hospital length of stay, 10 on mortality, 11 on nutrition and three on	☐	New Evidence: _____ _____ _____	☐

Figure D2. Informational letter for cancer (continued)

Conclusions From Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
weight. In pooled analyses, omega-3 fatty acids had no effect compared to placebo on post-operative complications, hospital length of stay, or mortality. With the exception of one study that demonstrated higher mean nitrogen intake for subjects treated with omega-3 fatty acids relative to placebo, no significant effect on nutrition or weight loss was observed.			
Effects on Clinical Outcomes after Cancer Treatment **Key Question 2b: What is the evidence that the response to omega-3 fatty acids is independent of the intake of antioxidants such as vitamin E or other bioactive food components?**			
No studies were identified that allowed this question to be answered.	☐	New Evidence: _____ _____ _____	☐
Effects on Clinical Outcomes after Cancer Treatment **Key Question 2c: What is the evidence that the response is modified by the state of the immune system?**			
No studies were identified that examined the possible modification of the effect of omega-3 fatty acids on clinical outcomes by immune status.	☐	New Evidence: _____ _____ _____	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

Cardiovascular Risk Factors

Figure D3. Informational letter for cardiovascular risk factors

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Total cholesterol (TC)			
23 RCTs (20 FO, 4 ALA) (N≥60 [parallel design], N≥40 [crossover]) 1. The studies "were heterogeneous, but mostly found small (0% to 6%), non-significant net increases in level of [total cholesterol]." 2. "The effect of plant oils (ALA) on [TC] was possibly weaker but similar to the effect of marine oils." 3. 19 fish oil (FO) studies: Summary net effect 0 (95% CI -1, +2) mg/dL; Higher mean baseline TC associated with larger net decrease in TC.[1] 4. 5 ALA studies: Range of net effects -1, +13 mg/dL[2] 5. No clear evidence of different effects in different populations 6. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of N-3 FA 7. No difference in effect seen across 5 weeks and 2 years of exposure. 8. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know**		
LDL cholesterol			
15 RCTs (14 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 9. "The effect of omega-3 fatty acid consumption was fairly uniform across studies. Most found a net increase in LDL with treatment." 10. "The effect of plant oils (ALA) on [LDL] was possibly weaker but similar to the effect of marine oils." 11. 13 fish oil studies: Summary net effect +6 (95% CI +3, +8) mg/dL[3] 12. 3 ALA studies: Range of net effects -2, +3 mg/dL[4] 13. No clear evidence of different effects in different populations 14. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of N-3 FA 15. No difference in effect seen across 8 weeks and 2 years of exposure. 16. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know**		

[1] Balk et al. Atherosclerosis. 189:19-30. 2006
[2] Balk et al. Atherosclerosis. 189:19-30. 2006
[3] Balk et al. Atherosclerosis. 189:19-30. 2006
[4] Balk et al. Atherosclerosis. 189:19-30. 2006

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
HDL cholesterol			
19 RCTs (18 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 17. The studies "were heterogeneous, but mostly found small (0% to 6%), non-significant net increases in level of [HDL]." 18. "The effect of plant oils (ALA) on [TC] was possibly weaker but similar to the effect of marine oils." 19. 17 fish oil studies: Summary net effect +1.6 (95% CI +0.8, +2.3) mg/dL[5] 20. 3 ALA studies: Range of net effects -1, +1 mg/dL[6] 21. No clear evidence of different effects in different populations 22. Inadequate or inconsistent evidence regarding covariates, dose, source, or type of N-3 FA 23. " No clear effect across [or within 5] studies… based on duration of intervention or exposure." 24. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know**		

[5] Balk et al. Atherosclerosis. 189:19-30. 2006

[6] Balk et al. Atherosclerosis. 189:19-30. 2006

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Triglycerides			
19 RCTs (18 FO, 2 ALA) (N≥60 [parallel design], N≥40 [crossover]) 25. "Most of [the] studies reported a net decrease in Tg of about 10% to 33%." "However, 1 of 2 studies of plant oils (ALA) found a net increase in Tg." 26. 17 fish oil studies: Summary net effect +27 (95% CI -33, -20) mg/dL; Higher baseline Tg and higher dose associated with larger effect.[7] 27. 3 ALA studies: Range of net effects -19, +23 mg/dL[8] 28. "The effect was… generally consistent among healthy subjects and patients with CVD, dyslipidemia, or at elevated risk of CVD." (No study of diabetic patients had sufficient number of subjects to be analyzed.) 29. "The effect was dose-dependent… [and] greater in studies with higher mean baseline Tg." 30. "Limited data suggest the effect is not related to sex, age, weight, background diet, or lipid treatment." 31. "The effect of duration of intervention is unclear." 32. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know**		
Lipoprotein (a) Lp(a)			
14 RCTs (13 FO, 1 ALA) (N≥5) 33. "No consistent effect on Lp(a) levels…. In approximately one-third of the studies the N-3 FA study arms had a net increase in Lp(a) level compared to control; in the remaining studies the net decrease in Lp(a) was generally small and non-significant." 34. No clear evidence of different effects in different populations 35. Evidence (in 2 studies directly, or across studies) of no different effects based on dose or based on exposure duration 36. Inadequate evidence regarding covariates, source or type of N-3 FA. 37. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

[7] Balk et al. Atherosclerosis. 189:19-30. 2006
[8] Balk et al. Atherosclerosis. 189:19-30. 2006

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Apolipoprotein A-1 apo A-1			
27 RCTs (27 FO, 1 ALA) (N≥20 [parallel design], N≥15 [crossover]) 38. The studies "generally found no effect or either a small increase or decrease in level with N-3 FA consumption." 39. "Limited evidence suggested that purified EPA may decrease apo A-1 levels while DHA has no effect, and that there is no difference in effect between fish oils and ALA." 40. No evidence of a dose effect or of different effects in different populations 41. One study reported no association in effect with sex, BMI, hypertension, and NIDDM. 42. Evidence (in 2 studies directly, or across studies) of no different effects based on exposure duration 43. Three studies followed subjects after stopping the intervention. One found a persistent decrease in apo A-1 at 5 months, but the other two studies found no difference (from baseline) after 8 weeks and 6 months.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		
Apolipoprotein B apo B			
25 RCTs (24 FO, 2 ALA) (N≥20 [parallel design], N≥10 [crossover]) 44. "Little consistency in the effect of N-3 FA on apo B levels. About half… found a small net increase and half a small net decrease." 45. In contrasts to studies of other populations, the 4 studies of people with diabetes all found "small, non-significant net increases in apo B." 46. One study found a significantly greater rise in apo B level in younger, compared to older, participants. A different study found no difference related to intake of saturated fats. 47. Two of three studies found larger net decreases in apo B with higher doses of fish oil or dietary fish intake, but this effect was not confirmed across studies. No consistent evidence regard differences among different sources of fish oils. 48. Inadequate evidence regarding effect of exposure duration. 49. In 3 studies, no clear evidence of any sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Apolipoprotein B-100 apo B-100			
4 RCTs (4 FO, 0 ALA) (N≥5) 50. No consistent effect. 51. Insufficient data to evaluate differences across populations. 52. One study found no correlation between change in apo B-100 and sex, BMI, hypertension, or diabetes. 53. Inadequate evidence regarding different effects based on source or dose. 54. Possible evidence of no difference in effect based on exposure duration 55. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		
LDL Apolipoprotein B LDL apo B			
6 RCTs (6 FO, 0 ALA) (N≥5) 56. Evidence suggests "large, [statistically] significant net increases in LDL apo B [of] 20-45 mg/dL." 57. Insufficient data to evaluate differences across populations. 58. One study found no correlation between change in LDL apo B and diet or body weight. 59. Inadequate evidence regarding different effects based on source or dose. 60. Possible evidence of no difference in effect based on exposure duration 61. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Blood pressure			
Pre-existing SR in people without DM (36 RCTs, all FO) 6 RCTs (6 FO, 0 ALA) (DM, N≥15 [parallel design], N≥10 [crossover]) SR in non-diabetics: 62. Summary net change SBP -2.1 (-3.2, -1.0) mm Hg, DBP -1.6 (-2.2, -1.0). 63. SBP and DBP reductions were significantly larger in studies with mean ages ≥45 y, mean BP ≥140/90. No association with mean BMI, trial duration, or fish oil dose. Unable to assess sex. RCTs of diabetics 64. "Generally small, non-significant effects on SBP and DBP", similar to meta-analysis of studies of non-diabetics 65. 1 study found no association between sex or Hb A1c and BP effect. No consistent differences across studies based on covariates. 66. Across studies no clear evidence of different effects based on dose, source, or duration of exposure to FO. 67. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know**		
Hemoglobin A_{1c}			
18 RCTs (18 FO, 0 ALA) (N≥10) 68. "N-3 FA had a very small, if any, effect on Hgb A1c levels compared to control." 69. Summary net effect 0.1% (95% CI -0.01, +0.2) ; Homogeneous.[9] 70. No clear difference across studies based on sub-populations 71. 1 study found no correlation in effect with diet or body weight. Another study found no difference between men and women. 72. 2 studies found no difference in effect based on dose. Also no evidence of a dose effect across studies. 73. 2 studies found no overall difference in effect at different time points. 74. 1 study found that Hgb A1c remained unchanged 8 weeks after stopping supplementation.	☐ **Yes** ☐ **No** ☐ **Do not know**		

[9] Balk et al. Atherosclerosis. 189:19-30. 2006

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Fasting glucose			
17 RCTs (18 FO, 0 ALA) (N≥25 [parallel design], N≥15 [crossover]) 75. "The effect of N-3 FA on [fasting glucose] was inconsistent across the studies." 76. Summary net effect 3.0 (95% CI -0.2, +6) mg/dL; Higher mean baseline fasting glucose and higher dose associated with larger net increases in fasting glucose.[10] 77. No clear difference across studies based on sub-populations 78. 3 studies found no correlations in effect with diet or body weight. 79. No evidence within or across studies suggesting differences based on source or dose (based on qualitative analysis). 80. 2 studies found no overall difference in effect at different time points. 81. 2 studies found that any changes in fasting glucose reverted to baseline after 8 or 12 weeks after stopping supplementation.	☐ **Yes** ☐ **No** ☐ **Do not know**		
Fasting insulin			
15 RCTs (18 FO, 0 ALA) (N≥5) 82. Baseline fasting insulin levels varied widely within and between studies, including differences between FO and placebo groups up to 60%. Across studies there was a very broad range of net percent changes in fasting insulin. 83. There was similar heterogeneity in effect in euglycemic and hyperglycemic populations. 84. 1 study of euglycemic participants found no interaction with weight loss (on a weight loss diet). No differences based on covariates could be discerned across studies. 85. No evidence suggests different effects based on dose or source. 86. 1 study reported no difference in effects at multiple time points to 6 months. 87. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

[10] Balk et al. Atherosclerosis. 189:19-30. 2006

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
C-reactive protein			
4 RCTs (4 FO, 0 ALA), 1 cross-sectional (Fish) (Any study) 88. No study found a significant effect of N-3 FA consumption on CRP level. 89. In one trial no difference in effect was seen among participants with elevated baseline CRP (>2 mg/L) 90. There was no evidence of a dose effect. 91. CRP levels were unchanged regardless of intervention duration up to 3 months. 92. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		
Fibrinogen			
24 RCTs (22 FO, 3 ALA) (N≥15 [parallel design], N≥10 [crossover]) 93. Across the studies there was no consistent effect on fibrinogen levels of N-3 FA consumption compared to control. 94. Subsets of studies evaluated healthy people, those with CVD or hypertension, those with dyslipidemia, and those with diabetes. No consistent difference in effect was seen across studies. However, two studies found a large net decrease in fibrinogen with N-3 FA in 10 subjects with hyperlipoproteinemia types IIb or IV, and a significant net increase in those with insulin-dependent diabetes, respectively. 95. Five studies found no association in effect with various factors including sex, baseline and change in weight, baseline blood pressure, changes in lipids or insulin, or cardiovascular, lipid or antithrombotic drug use, wine consumption, high- or low-fat diets. 96. There was no consistent dose effect or difference by source of N-3 FA 97. There was no apparent difference in effect across 2 weeks to 2 years of consumption. 98. Two studies, which found no effect on fibrinogen, also found no further change 4 weeks or 6 months after stopping the intervention.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Factor VII			
19 RCTs (17 FO, 3 ALA) (N≥15 [parallel design], N≥10 [crossover]) 99. There was no consistency in effect across studies. Any net changes were small (<7%). 100. Two of three studies of people with diabetes found a statistically significant net increase in factor VII. No consistent effects were found in different populations. 101. Possible associations between effect size and covariates were analyzed by 3 studies, but there were no consistent findings. 102. Across studies, there was no evidence of a dose effect. Within studies there was no evidence of different effects with different N-3 FA sources. 103. Across studies, duration of intervention had no effect. 104. In one study, there continued to be no effect on factor VII 1 month after stopping the intervention.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		
Factor VIII			
5 RCTs (4 FO, 1 ALA) (N≥5) 105. There was no consistency in effect across studies. 106. The single stuffy of insulin dependent diabetics found a larger, though non-significant net increase of factor VIII than studies of the general population. 107. One study found no association between effect size asnd sex or Hgb A1c in insulin dependent diabetics who were also taking aspirin. 108. One study found no fish oil dose effect. The evidence across studies was unclear regarding differential effects based on source or type of N-3 FA. 109. Three studies found no consistent effect across a range of intervention durations from 3 weeks to 12 months. 110. In one study there was no change in factor VIII 1 and 2 months after stopping the intervention.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
von Willebrand Factor (vWF)			
9 RCTs (8 FO, 1 ALA) (N≥5) 111. Most studies found a net decrease in vWF (up to 13%), though only one study found a statistically significant difference. 112. No clear pattern in effect was seen across populations. 113. The studies do not allow conclusions about the effect of covariates. 114. One study each found no dose effect and no difference between fish oil type. There was no consistent effect based on dose or type across studies. 115. Two studies found no consistent effect across a range of intervention durations from 3 weeks to 12 months. 116. In one study there was no change in factor VIII 1 and 2 months after stopping the intervention.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Platelet aggregation			
11 RCTs (8 FO, 5 ALA) (N≥15 [parallel design], N≥10 [crossover]) 117. There was a great deal of heterogeneity of the methods for determining platelet aggregation. 118. "Heterogeneous effects were generally found depending on the aggregating agent, the dose of the agent, and the measurement metric used. However, in most studies either no effect on platelet aggreagation was found with N-3 FA or no difference in effect was seen between treatments and controls." 119. There was no evidence suggestive of differential effects in different populations – including by health status, weight, age, or sex – or covariates – including smoking and alcohol consumption, both within and across studies. 120. No study compared different doses of N-3 FA. No dose effect was seen across studies. Two studies disagreed whether platelet aggregation differed with fish oil or ALA. One concluded that pure DHA is less potent at reducing aggregation than fish oil or dietary fish at moderate doses. 121. No clear effect of time consuming N-3 FA was seen in 3 studies. 122. One study found that one measure of platelet aggregation did not return to baseline during a 12 week follow-up after stopping the trial; though other tests did.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Coronary arteriography			
12 RCTs (12 FO, 0 ALA) (N≥5) 123. "Overall, although there is heterogeneity among studies, there is a trend toward a net reduction of coronary artery restenosis with fish oil supplementation." Random effects model RR = 0.86 (95% CI 0.71, 1.03). 124. All studies included patients undergoing PTCA. The studies that performed multivariate analyses including diabetes, lipid and cardiovascular variables generally found no association between these covariates and restenosis rates. Two studies found no difference between men and women. 125. The heterogeneity of the studies was not explained by either dose or treatment duration. 126. No evidence on sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know**		
Carotid intima media thickness (IMT)			
1 RCT (FO), 1 longitudinal cohort (ALA), 2 cross-sectional (1 dietary ALA, 1 fishing vs farming village) (Any study) 127. The only RCT of fish oil found no significant net effect on carotid IMT. The longitudinal study of ALA was consistent with the RCT. The cross sectional studies both found that higher N-3 FA intake was associated with thinner IMT. 128. Insufficient evidence to evaluate subpopulations, covariates, dose effect, source effect, exposure duration, or sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		
Exercise tolerance testing			
3 RCTs (3 FO, 0 ALA), 3 longitudinal cohorts (3 FO, 0 ALA) (Any study) 129. The studies suggest that fish oil consumption may benefit exercise capacity among patients with coronary artery disease, although the effect may be small. 130. Insufficient evidence to evaluate subpopulations, covariates, dose effect, source effect, exposure duration, or sustainment of effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		

Figure D3. Informational letter for cardiovascular risk factors (continued)

Updating *Effects of N-3 FA on CV Risk Factors and Intermediate Outcomes of CVD*

Findings of Original Report **No. & Type of Studies, by Intervention (Eligibility criteria)**	**Are all of these findings almost certainly still supported by the evidence?**	**What statement has new evidence of a different conclusion (# from list of statements)?**	**What is the new evidence (with citations, if possible)?**
Heart rate variability			
2 RCTs (2 FO, 0 ALA), 1 cross-sectional (FO) (Any study) 131. The 3 studies, all by the same set of investigators, found that there was no significant effect of fish oil on heart rate variability in healthy volunteers, but may increase (improve) heart rate variability in survivors of myocardial infarction. 132. There is possible evidence of a dose effect.	☐ **Yes** ☐ **No** ☐ **Do not know** ☐ **Do not update this outcome**		
Are there other cardiovascular risk factors or intermediate markers of cardiovascular disease that you know of that should be reviewed in a future report on omega-3 fatty acids? *(If yes, please list them in the last column)*			
	☐ **Yes** ☐ **No** ☐ **Do not know**		

Comments

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