

Supplemental Table 1. Key questions addressed by original systematic reviews

Evidence Review	Key Questions
Cognitive Function Review (10)	<p>What is the evidence that omega-3 FA play a role in maintaining cognitive function in normal aging?</p> <p>What is the evidence that omega-3 FA affect the incidence of dementia including Alzheimer's disease?</p> <p>What is the evidence that omega-3 FA are effective in the treatment of dementia including Alzheimer's disease?</p> <p>What is the evidence that omega-3 FA affect the incidence of OTHER neurological diseases?</p> <p>What is the evidence that omega-3 FA prevent the progression of multiple sclerosis?</p>
Cancer Review (11)	<p>What is the evidence that omega-3 fatty acids reduce the incidence of tumors? For what type of tumors?</p> <p>If omega-3 fatty acids influence the incidence of tumors, is there an inverse relationship with intake?</p> <p>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?</p> <p>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?</p> <p>What is the evidence that the response is modified by the state of the immune system?</p> <p>What is the evidence that omega-3 fatty acids alter the effects of cancer treatment on malignant tumors and clinical outcomes after cancer treatments?</p> <p>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?</p> <p>What is the evidence that the response is modified by the state of the immune system?</p>
Cardiovascular Intermediate Outcomes and Risk Factors Review (12)	<p>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)?</p> <p>How do the effects differ by</p> <ul style="list-style-type: none"> • Dose • Duration of intake • Specific omega-3 fatty acid (or their ratios) • Source (eg, 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 <ul style="list-style-type: none"> ○ 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?

Supplemental Table 2. Form sent to domain experts for omega-3 fatty acid and cognitive function

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.	<input type="checkbox"/>	New Evidence: _____ _____ _____	<input type="checkbox"/>
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.	<input type="checkbox"/>	New Evidence: _____ _____ _____	<input type="checkbox"/>
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.	<input type="checkbox"/>	New Evidence: _____ _____ _____	<input type="checkbox"/>

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 4: What is the evidence that omega-3 FA affect the incidence of neurological diseases?			
<p>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 associated with a lower risk.</p>	<input type="checkbox"/>	<p>New Evidence:</p> <hr/> <hr/> <hr/>	<input type="checkbox"/>
Key Question 5: What is the evidence that omega-3 FA prevent the progression of multiple sclerosis?			
<p>Three studies 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, 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.</p>	<input type="checkbox"/>	<p>New Evidence:</p> <hr/> <hr/> <hr/>	<input type="checkbox"/>
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

Supplemental Table 3. Example of form sent to domain experts for omega-3 fatty acid and 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
<p>Key Question 1: Effect of Tumor Incidence</p>			
<p>Key Question 1a: What is the evidence that omega-3 fatty acids reduce the incidence of tumors (in humans)? For what type of tumors?</p>			
<p>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.</p> <p>Significant associations between omega-3 consumption and cancer risk were reported:</p> <ul style="list-style-type: none"> • for lung cancer in two studies; • for breast cancer in one; • for prostate cancer in one; and • for skin cancer in one. <p>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.</p>	<input type="checkbox"/>	<p>New Evidence:</p> <hr/> <hr/> <hr/>	<input type="checkbox"/>
<p>Key Question 1b: If omega-3 fatty acids influence the incidence of tumors, is there an inverse relationship with intake?</p>			
<p>Data were insufficient to permit assessment of a dose-response relationship.</p>	<input type="checkbox"/>	<p>New Evidence:</p> <hr/> <hr/> <hr/>	<input type="checkbox"/>

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
<p>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?</p>			
<p>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.</p> <p>We did not identify any studies that assessed the effects of omega-3 fatty acids on clinical outcomes after chemotherapy or radiation surgery.</p> <p>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.</p> <p>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.</p>	<input type="checkbox"/>	<p>New Evidence:</p> <hr/> <hr/> <hr/>	<input type="checkbox"/>
<p>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?</p>			
<p>No studies were identified that allowed this question to be answered.</p>	<input type="checkbox"/>	<p>New Evidence:</p> <hr/> <hr/> <hr/>	<input type="checkbox"/>
<p>Are there new data that could inform the key questions that might not be addressed in the conclusions?</p>			

Supplemental Table 4. Example of form sent to domain experts for omega-3 fatty acid and cardiovascular intermediate outcomes and risk factors

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)?
<i>Total cholesterol (TC)</i>			
<p>23 RCTs (20 FO, 4 ALA) (N≥60 [parallel design], N≥40 [crossover])</p> <ol style="list-style-type: none"> 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/dL¹ 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. 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Do not know		

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)?
<i>LDL cholesterol</i>			
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 ¹ 12. 3 ALA studies: Range of net effects -2, +3 mg/dL ¹ 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.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Do not know		
<i>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)</i>			
	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Do not know		

¹ Balk et al. Atherosclerosis. 189:19-30. 2006

Supplemental Figure. Summary of the Ottawa method [8]

