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Abstract

Objective To review systematically the evidence for an effect of long chain and shorter chain omega 3 fatty acids on total mortality, cardiovascular events, and cancer.

Data sources Electronic databases searched to February 2002; authors contacted and bibliographies of randomised controlled trials (RCTs) checked to locate studies.

Review methods Review of RCTs of omega 3 intake for ≥ 6 months in adults (with or without risk factors for cardiovascular disease) with data on a relevant outcome. Cohort studies that estimated omega 3 intake and related this to clinical outcome during at least 6 months were also included. Application of inclusion criteria, data extraction, and quality assessments were performed independently in duplicate.

Results Of 15 159 titles and abstracts assessed, 48 RCTs (36 913 participants) and 41 cohort studies were analysed. The trial results were inconsistent. The pooled estimate showed no strong evidence of reduced risk of total mortality (relative risk 0.87, 95% confidence interval 0.73 to 1.03) or combined cardiovascular events (0.95, 0.82 to 1.12) in participants taking additional omega 3 fats. The few studies at low risk of bias were more consistent, but they showed no effect of omega 3 on total mortality (0.98, 0.70 to 1.36) or cardiovascular events (1.09, 0.87 to 1.37). When data from the subgroup of studies of long chain omega 3 fats were analysed separately, total mortality (0.86, 0.70 to 1.04; 138 events) and cardiovascular events (0.93, 0.79 to 1.11) were not clearly reduced. Neither RCTs nor cohort studies suggested increased risk of cancer with a higher intake of omega 3 (trials: 1.07, 0.88 to 1.30; cohort studies: 1.02, 0.87 to 1.19), but clinically important harm could not be excluded.

Conclusion Long chain and shorter chain omega 3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer.

Introduction

Consumption of long chain omega 3 fatty acids (eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA)) found in fatty fish and fish oils has been linked to the low incidence of coronary heart disease in the Inuit people of Greenland¹; α linolenic acid (ALA), a shorter chain omega 3 found in some plant oils (and variably converted to eicosapentaenoic acid and docosahexaenoic acid) may also be protective.²

Toxic compounds, such as fat soluble methylmercury, dioxins, and polychlorinated biphenyls, are

also found in oily fish and fish oils, but any harm from these compounds would be seen only after long term supplementation. Animal intervention studies and studies of adults after severe inadvertent exposure indicate that dioxins and polychlorinated biphenyls increase the risk of cancer. Methylmercury may increase the risk of myocardial infarction and cause neurological damage.

Since a meta-analysis of the effect of omega 3 fats on cardiovascular morbidity and mortality in coronary heart disease suggested important benefits,³ a large intervention study has been published.⁴ Our meta-analysis included these new data, balanced protective effects with possible harm, assessed the effects of plant based omega 3 fats on health, and included people without established cardiovascular disease, and highlights important questions about the role of omega 3 fats on cardiovascular disease and mortality. We systematically reviewed the effects of long chain and short chain omega 3 fats (together and separately) on mortality, cardiovascular disease, cancer, and bleeding events and analysed all relevant randomised controlled trials (RCTs) and prospective cohort studies.

Methods

Study methods are described elsewhere.⁵

Search strategy and study selection

We searched the Cochrane Library, Medline, Embase, the National Research Register, and SIGLE (to February 2002); we checked the bibliographies of included studies and contacted the authors. Articles not in English were translated. See bmj.com for exclusion criteria, methods of data extraction, and assessment of quality of studies.

Data synthesis

For RCTs we extracted the numbers of participants experiencing each outcome and total numbers randomised for each study arm and combined them, using relative risks in random effects meta-analysis. For cohort studies we used relative risk or odds ratio that had been adjusted for the most confounding factors, and compared the most exposed quantile with the least exposed quantile. We used one analysis only for each cohort per outcome.

In the RCTs we used the subgroups of long chain versus short chain omega 3 fats and dietary advice versus supplementation to analyse the effects on



A complete set of references is available on bmj.com.



This is the abridged version of an article that was posted on bmj.com on 24 March 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38755.366331.2F>

mortality, cardiovascular events, and cancer. We used random effects meta-regression to analyse the effects of the dose of omega 3 and the duration of the trial. Sensitivity analyses assessed the robustness of RCT results to trial quality by restricting the analysis to studies with low risk of bias. We also quantified inconsistency between studies using I^2 (see bmj.com).

Results

We screened 15 159 titles and collected 926 full text papers. Forty eight randomised controlled trials and 41 analyses of 26 cohort studies fulfilled all inclusion criteria; for references and main characteristics of trials see bmj.com.

Intervention or exposure

Dietary supplements were given in 44 trials (36 as capsules, six as oil, one each as liquid emulsion and enriched margarine), advice on eating oily fish in three, and advice on diet and food supplements in one. Supplements were long chain omega 3 fats (usually whole or concentrated fish oil; one small trial used refined eicosapentaenoic acid and one used refined docosahexaenoic acid), and five studies provided shorter chain omega 3 fats. Doses of long chain omega 3 fats (summing eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid) varied from 0.4 g to 7.0 g per day. Control groups received vegetable oils, other fats, "inert" or ill defined substances, different dietary advice, or nothing. The intervention lasted 6-11 months in 23 studies, 12-23 months in 16, 24-47 months in eight, and ≥ 48 months in one study.

Intake of omega 3 (varying combinations of eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid, along with α linolenic acid, supplemental fish oils, or dietary oily fish) was assessed by dietary and biochemical means in two cohorts, dietary means only in 18, and biochemical means only in 10. Groups with the lowest and highest intake of long chain omega 3 differed by 0.1-0.6 g omega 3 a day.

Methodological quality

Twenty five RCTs were rated as having a low risk of bias (see bmj.com). Losses to follow-up were unclear in 16 cohort studies. In 15 cohort studies the outcome assessors were masked to exposure, in two they were not masked, and in nine masking was unclear.

In the seven cohort studies that described omega 3 intake at baseline (five assessed long chain omega 3 fats only, one short chain omega 3 fats only, and one assessed both) the characteristics of participants with high and low intake of omega 3 fats differed. People who consumed most long chain omega 3 at baseline had an advantage with regard to lifestyle (smoking, diet, and exercise), interest in health, and social factors (education, living in town). Adjustment for these potential confounding factors may not have been adequate.

Total mortality

Deaths occurred in 15 RCTs (1995 deaths), and authors of 29 reported that no deaths occurred. Evidence that risk of death was reduced in participants randomised to omega 3 (relative risk 0.87, 95% confidence interval 0.73 to 1.03) was weak, and inconsistency was moderate ($I^2=42\%$) (figure) (see bmj.com).

When analysis was restricted to studies at low risk of bias this effect was attenuated (0.98, 0.70 to 1.36; 138 deaths), and inconsistency between RCTs was low ($I^2=0\%$). This sensitivity analysis removed one RCT whose studies have been questioned.

Results were similar for long chain versus short chain omega 3 and dietary advice versus supplements. Meta-regression indicated that the risk of death increased as the length of the RCT increased (regression coefficient 0.008, 0.003 to 0.012). This is compatible with omega 3 fats having an early protective effect that later becomes harmful; however, the association was lost when we removed the large trial by Burr et al.⁴ Meta-regression did not suggest a relation between mortality and the dose of long chain omega 3. Cohort studies suggested that omega 3 protected against death (0.65, 0.48 to 0.88; $I^2=36\%$), but it was unclear whether adjustment for confounders was adequate.

Combined cardiovascular events

Eighteen RCTs provided data on cardiovascular events in 2628 participants. The meta-analysis showed no definite effect of omega 3 fats on cardiovascular events, but confidence intervals were wide (0.95, 0.82 to 1.12) and inconsistency was high ($I^2=65\%$). Removing studies at moderate or high risk of bias reduced but did not remove inconsistency (1.09, 0.87 to 1.37; 570 events; $I^2=49\%$).

Subgrouping by long chain versus short chain omega 3 or by advice to eat oily fish versus supplements did not generate robust effects of omega 3 fats on cardiovascular events. Cohort studies provided no strong evidence that omega 3 fats protect against cardiovascular events.

Cancer

Ten RCTs reported the incidence of cancer; 391 diagnoses of cancer or death from cancer occurred in 17 433 participants and two of the trials reported no cancers. We found no evidence that omega 3 fats had an effect on the incidence of cancer (1.07, 0.88 to 1.30) and inconsistency was not seen ($I^2=0\%$) (see bmj.com). Five trials and seven events remained after sensitivity analysis.

Seven cohort studies provided data on cancer (832 events in the highest and lowest quantiles), and meta-analysis found no effect of high versus low intake of omega 3 (1.02, 0.87 to 1.19; $I^2=21\%$).

Outcomes related to bleeding

Nine RCTs reported at least one stroke (243 strokes in total), but little information was available specifically on haemorrhagic stroke. Omega 3 had no clear effect on strokes (1.17, 0.91 to 1.51; $I^2=0\%$), in sensitivity analysis (29 events), or in four cohort studies (0.87, 0.72 to 1.04) (see bmj.com).

Discussion

Our meta-analysis of RCTs assessing the effects of increased omega 3 fats on total mortality found substantial variations between studies. Studies with stronger methodology had more consistent results, and the pooled relative risk of these studies was 0.98 (0.70 to 1.36; 138 events). We found no evidence from RCTs or cohort studies that omega 3 fats have an effect

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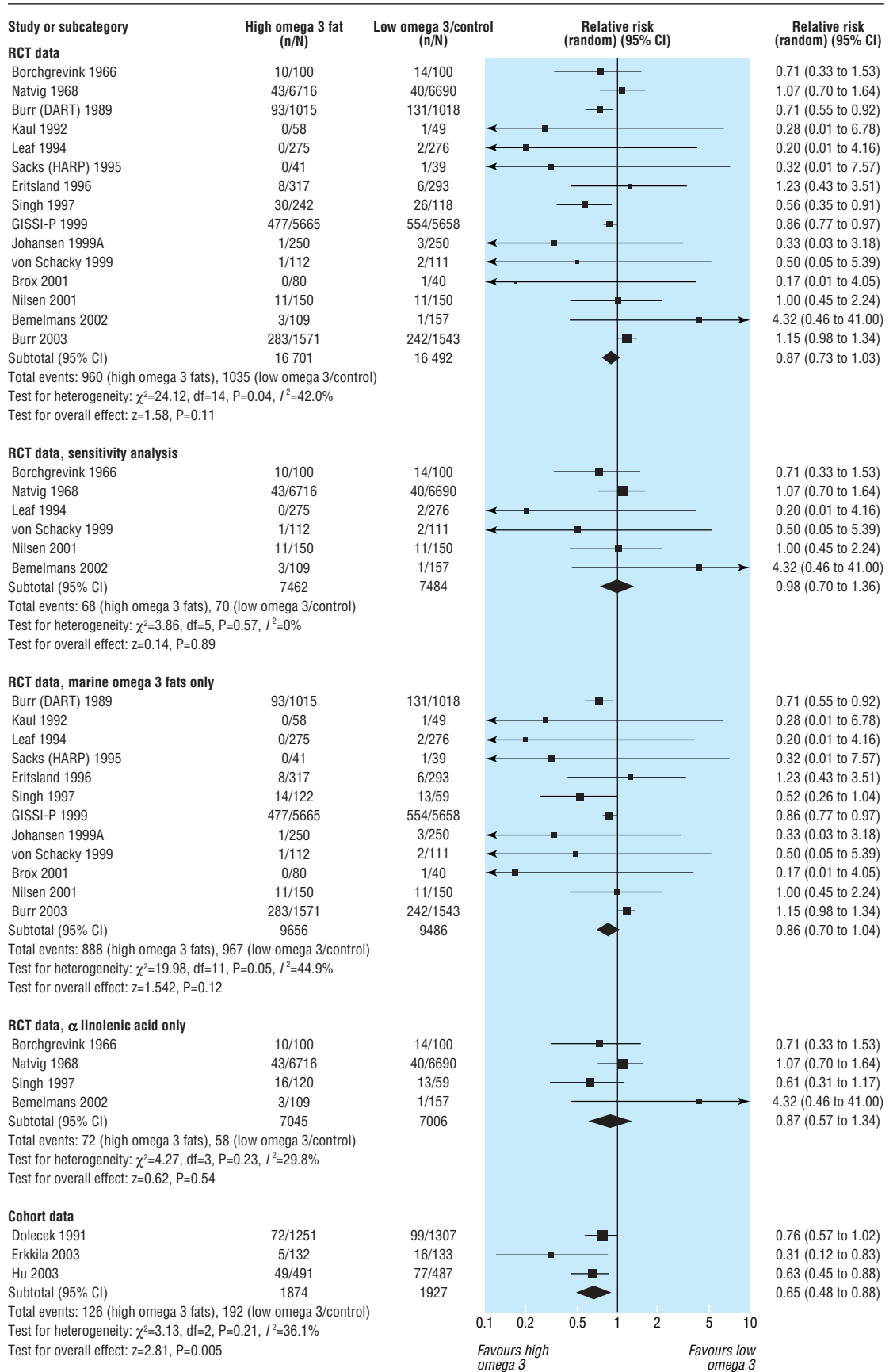
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Effect of omega 3 fatty acids on mortality. For references see bmj.com

on combined cardiovascular events. Neither RCTs nor cohort studies showed significantly increased risks of cancer or stroke with higher intake of omega 3, but there were too few events to rule out important effects.

Strengths and weaknesses

The largest studies reviewed had greater potential for bias than some of the smaller ones. We hoped that pooling studies at low risk of bias might provide enough power to inform us of effects on health, but this was not the case. Similarly, analysis of the effects of omega 3 on rarer outcomes such as stroke had insufficient power to detect clinically important effects. Unlike previous meta-analyses, we reviewed systematically the effects of omega 3 fats on mortality, cardiovascular disease, cancer, and bleeding events and analysed all relevant RCTs and prospective cohort studies. We also accounted for differences in study quality and examined the effects of long chain and short chain omega 3 fats in a wide group of participants; this provides high quality evidence to guide policy and practice.

Other studies

Our findings differ from those of a recent systematic review by Bucher et al,³ which reviewed trials assessing the effects of long chain omega 3 fats over at least six months in patients with coronary heart disease and found significant protection from mortality and sudden death. It did not include the large recent study by Burr et al.⁴

Possible explanations for the differences in results between this and the Bucher review rests on our inclusion of the study by Burr et al. These are that this RCT had the longest follow-up of all RCTs and the harmful effects of methylmercury could be cumulative; the study was the only RCT that specifically enrolled men treated for angina; omega 3 from oily fish has a different effect to fish oil supplements (but this was found not to explain the differences); the effect of omega 3 fats on cardiovascular disease is smaller than previously thought; or that its beneficial effect is limited to a specific group (such as patients after myocardial infarction or with heart failure) (see bmj.com). Two other systematic reviews were less comprehensive than ours.^{6,7}

Interpretation

It is not clear whether long chain or short chain omega 3 fats (together or separately) reduce or increase total mortality, cardiovascular events, cancer, or strokes. Our findings do not rule out an important effect of omega 3 fats on total mortality, as robust trials at low risk of bias reported few deaths. The source (dietary or supplemental) and dose of omega 3 fats did not seem to affect the effectiveness of long chain omega 3 fats.

UK guidelines encourage the general public to eat more oily fish, and higher amounts are advised after myocardial infarction (supported by trials after myocardial infarction). This advice should continue at present, but the evidence should be reviewed regularly. It is probably not appropriate to recommend a high intake of omega 3 fats for people who have angina but have not had a myocardial infarction.

Thanks to Theresa Moore and Margaret Burke from the Cochrane Heart Group, and to all of the authors of primary studies who helped us build up the data. This paper is based on a Cochrane review accepted for publication in The Cochrane Library (see www.TheCochraneLibrary.net for information).

What is already known on this topic

A systematic review of randomised controlled trials in coronary heart disease showed reduced mortality in patients taking supplemental long chain omega 3 fats

What this study adds

This systematic review assessed the health effects of long chain and shorter chain omega 3 fats (together or separately) on total mortality, cardiovascular events, cancer, and strokes in a wide group of participants and found no evidence of a clear benefit of omega 3 fats on health

Contributors: See bmj.com.

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Competing interests: NEC has received fees for speaking from Solvay Healthcare, who market Omacor.

Ethical approval: Not required.

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Corrections and clarifications

ABC of wound healing: Burns

We failed to spot an obvious error in this article by Alex Benson and colleagues (*BMJ* 2006;332:649-52, 18 Mar). In the box titled "Criteria for referral to a burns centre" (p 651), the three "less than" symbols (for proportion of total body surface area affected by partial or full thickness burns) should of course have been "more than" symbols.

Call to scrap import tariffs on pharmaceuticals in global WTO talks

In this news article by John Zarocostas, we wrongly stated that a proposal calling for an end to import tariffs was circulated during talks in Doha, Qatar (*BMJ* 2006;332:508, doi:10.1136/bmj.332.7540.508-c). In fact the talks were in Geneva.

Obituaries: Kenneth Herbert Walter

In this obituary, we wrongly spelt Kenneth Walter's name as Walker (*BMJ* 2006;332:671, 18 Mar). We have not been able to discover how we made this mistake, but we do apologise.