Long chain omega-3 fatty acids and cardiovascular disease: a systematic review

Javier Delgado-Lista1,2†, Pablo Perez-Martinez1,2†, Jose Lopez-Miranda1,2 and Francisco Perez-Jimenez1,2*

1Lipids and Atherosclerosis Unit, Department of Medicine, IMIBIC/Hospital Universitario Reina Sofia/Universidad de Cordoba, Cordoba, Spain
2CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain

Abstract

Introduction: Cardiovascular disease remains the commonest health problem in developed countries, and residual risk after implementing all current therapies is still high. The use of marine omega-3 fatty acids (DHA and EPA) has been recommended to reduce cardiovascular risk by multiple mechanisms. Objectives: To update the current evidence on the influence of omega-3 on the rate of cardiovascular events. Review Methods: We used the MEDLINE and EMBASE databases to identify clinical trials and randomized controlled trials of omega-3 fatty acids (with quantified quantities) either in capsules or in dietary intake, compared to placebo or usual diet, equal to or longer than 6 months, and written in English. The primary outcome was a cardiovascular event of any kind and secondary outcomes were all-cause mortality, cardiac death and coronary events. We used RevMan 5·1 (Mantel-Haenszel method). Heterogeneity was assessed by the I² and Chi² tests. We included 21 of the 452 pre-selected studies. Results: We found an overall decrease of risk of suffering a cardiovascular event of any kind of 10 % (OR 0·90; [0·85–0·96], \( p = 0·001 \)), a 9 % decrease of risk of cardiac death (OR 0·91; [0·83–0·99]; \( p = 0·03 \)), a decrease of coronary events (fatal and non-fatal) of 18 % (OR 0·82; [0·75–0·90]; \( p < 1 \times 10^{-4} \)), and a trend to lower total mortality (5 % reduction of risk; OR 0·95; [0·89–1·02]; \( p = 0·15 \). Most of the studies analyzed included persons with high cardiovascular risk. Conclusions: marine omega-3 fatty acids are effective in preventing cardiovascular events, cardiac death and coronary events, especially in persons with high cardiovascular risk.

Key words: omega 3; n3; cardiovascular disease

Out of all the proposed beneficial effects on health of long chain omega-3 fatty acids, those affecting cardiovascular disease are, nowadays, those that receive more attention in clinical medicine. Evidence from epidemiological, observational and clinical trial studies have led the American Heart Association (AHA) to recommend their consumption, and thus omega-3 fatty acids have emerged as real players in the prevention of cardiovascular (mainly coronary) events\(^ {1,2}\). These recommendations include two servings of blue fish a week for the general population (to achieve a mean of 500 mg/d), and 1 g/d of marine omega-3 (EPA and DHA) in patients with coronary disease. As the contribution of omega-3 in the diet of many Western countries is far below the recommended figures, there is a clear need to increase their consumption. Although the inclusion of novel agents in the therapeutic guidelines of the AHA scientific committee is reserved for those interventions whose effectiveness and safety is beyond all doubt, controversial results have been published in recent reviews and meta-analysis reporting both positive and negative findings on the effectiveness of omega-3 fatty acids\(^ {3–6}\).

Research into omega-3 fatty acids has evolved from studies where their activity was tested, to a more complex scenario, where authors look for the potential underlying mechanisms that may be causing these effects. In other words, authors have switched from a perspective in which they treated to show the effects of omega-3 to another in which they aim to show how they work. Furthermore, this may lead to a bias when trying to evaluate the efficacy of the intervention, which is theoretically yet to be proven. Scientists may well think that journals are not very eager to include articles that show ‘again’ that omega-3 fatty acids are effective, instead of why they are so. Actually, research in this field is extremely active in this moment. A prior examination of the studies reported in PubMed regarding omega-3 fatty acids and cardiovascular disease or cardiovascular risk factors accounted for more than seventy thousand items. Over the last four years, the production of such studies has doubled (Fig. 1). In this extremely active context, is therefore not surprising that those studies that summarize the overall scientific information available at a given moment tend to modify their opinion depending on the articles included.

*Corresponding author: F. Perez-Jimenez, fax +34 957 204763, email fperezjimenez@uco.es
† Javier Delgado-Lista and Pablo Perez-Martinez contributed equally to the production of this article.
In the present review, we will summarize the information available as of January 20th, 2012, on the effects of omega-3 fatty acids on cardiovascular events, evaluating the evidence from clinical trials and randomized controlled trials. With this purpose in mind, we will conduct a search for recent reviews and meta-analysis, and a primary search for original clinical trials and randomized controlled trials.

Material and methods

The research question applied to the systematic review was ‘Are marine omega-3 fatty acids useful for reducing the incidence of total death, cardiovascular death coronary events or cardiovascular events?’ This article is limited to long chain (also called marine) omega-3. We did not review the effects of other omega-3 fatty acids. We focused only on clinical trials and randomized controlled trials. We limited our search to trials with a follow-up of 6 months or more.

Types of outcome measurements

Primary outcome. Odds ratio of cardiovascular events (defined as stroke, coronary events, myocardial infarction or angina, peripheral limb disease event or death from cardiovascular causes).

Secondary outcomes. Odds ratio for total mortality, cardiac death or total coronary events (both fatal and non-fatal).

Search methods for identification of studies

The search strategy for the identification of the studies is summarized in Fig. 2. The review included articles written in English, and published before January 20th, 2012. We used the two most commonly used electronic databases (Medline via PubMed and EMBASE), and combined search terms for omega-3 fatty acids (Omega-3 OR omega 3 OR polyunsaturated fatty acid OR pufa OR eicosapentanoic acid OR EPA OR ethyl eicosapentaenoic acid OR eepa OR docosahexanoic...
against the Jadad Scale for quality score(7). A score equal or
tinent or non-pertinent. Pertinent articles were measured
the first search (J. D-L and P. P-M) rated all the articles as per-
any exclusion criteria.

Studies which met the inclusion criteria and did not fulfill
aged 18 years or older who were involved in any of the
tric, oncological, gynecologic, renal, neurological or psychia-
estimated in g/d.

synergy with omega-3.

another concomitant treatment, not applied to the group not
receiving omega-3.

Studies in which the methodology described in the title/
abstract showed critical concerns.

When analyzing reviews and meta-analyses, the authors
decided whether the item was pertinent or not, based on
the title and abstract reading. If pertinent, the referenced
articles included in the item (review or meta-analysis) were
passed to the list of potential articles to include in this
review. When evaluating the clinical trials and randomized
controlled trials, the authors made an initial decision on the
pertinence of the article and whether it should remain on
the list based on the title and abstract reading, with the follow-
including inclusion and exclusion criteria:

(1) **Inclusion criteria.** Randomized controlled trials and
clinical trials which directly assessed the impact of the intake
of measured quantities of marine omega-3 fatty acids (either
in the form of foods or supplements or capsules) on any of
the MeSH terms used for defining clinical outcomes, for at
least 6 months.

Studies which reported total deaths and, at least, one of the
following: Cardiovascular mortality, acute (fatal and/or non-
fatal) myocardial infarction (AMI), angina, revascularization,
stroke (fatal and/or non-fatal), left ventricle function.

(2) **Exclusion criteria.** Articles written in languages other
than English.

Sub-studies of other studies that qualify for inclusion.

Studies in which α-linolenic acid (ALA) was present as an
active means of treatment.

Studies in which the methodology described in the title/
abstract showed critical concerns.

Studies in which the omega-3 fatty acids were part of
another concomitant treatment, not applied to the group not
receiving omega-3.

Studies in which another active treatment was tested in
synergy with omega-3.

Studies in which the intake of omega-3 was not measured or
estimated in g/d.

Studies limited to populations with ophthalmologic, obstet-
ic, oncological, gynecologic, renal, neurological or psychia-
tric disorders.

(3) **Eligibility.** Eligible patients were men and women
aged 18 years or older who were involved in any of the
studies which met the inclusion criteria and did not fulfill
any exclusion criteria.

The two authors who validated the studies that appeared in
the first search (J. D-L and P. P-M) rated all the articles as per-
tinent or non-pertinent. Pertinent articles were measured
against the Jadad Scale for quality score(7). A score equal or
lower to 2/5 in the Jadad score led to the article’s withdrawal
from the list. Where only one of the authors rated the article as
pertinent, a third author (F. P-J) rated the article, and decided
on the pertinence.

**Study selection**

When analyzing reviews and meta-analyses, the authors
decided whether the item was pertinent or not, based on
the title and abstract reading. If pertinent, the referenced
articles included in the item (review or meta-analysis) were
passed to the list of potential articles to include in this
review. When evaluating the clinical trials and randomized
controlled trials, the authors made an initial decision on the
pertinence of the article and whether it should remain on
the list based on the title and abstract reading, with the follow-
including inclusion and exclusion criteria:

(1) **Inclusion criteria.** Randomized controlled trials and
clinical trials which directly assessed the impact of the intake
of measured quantities of marine omega-3 fatty acids (either
in the form of foods or supplements or capsules) on any of
the MeSH terms used for defining clinical outcomes, for at
least 6 months.

Studies which reported total deaths and, at least, one of the
following: Cardiovascular mortality, acute (fatal and/or non-
fatal) myocardial infarction (AMI), angina, revascularization,
stroke (fatal and/or non-fatal), left ventricle function.

(2) **Exclusion criteria.** Articles written in languages other
than English.

Sub-studies of other studies that qualify for inclusion.

Studies in which α-linolenic acid (ALA) was present as an
active means of treatment.

Studies in which the methodology described in the title/
abstract showed critical concerns.

Studies in which the omega-3 fatty acids were part of
another concomitant treatment, not applied to the group not
receiving omega-3.

Studies in which another active treatment was tested in
synergy with omega-3.

Studies in which the intake of omega-3 was not measured or
estimated in g/d.

Studies limited to populations with ophthalmologic, obstet-
ic, oncological, gynecologic, renal, neurological or psychia-
tric disorders.

(3) **Eligibility.** Eligible patients were men and women
aged 18 years or older who were involved in any of the
studies which met the inclusion criteria and did not fulfill
any exclusion criteria.

The two authors who validated the studies that appeared in
the first search (J. D-L and P. P-M) rated all the articles as per-
tinent or non-pertinent. Pertinent articles were measured
against the Jadad Scale for quality score(7). A score equal or
lower to 2/5 in the Jadad score led to the article’s withdrawal
from the list. Where only one of the authors rated the article as
pertinent, a third author (F. P-J) rated the article, and decided
on the pertinence.

**Study analysis**

Statistical analysis was performed using Review Manager
5-017 (Cochrane Collaboration, Oxford, UK). We assessed
heterogeneity between studies using Chi² indicating signifi-
cant heterogeneity and I² with suggested thresholds for low
(25%–49%), moderate (50%–75%), and high (>75%) values. We used the fixed effects model as default, and the
random effects model when heterogeneity between studies
was high for the end point of interest. For all analyses, we
considered p ≤ 0.05 (2-sided) as significant. Summary effect
estimates are presented as an odds ratio (OR) with 95% con-
fidence intervals (CI). Overall effect was assessed by the Z test.
We used the Mantel-Haenszel statistical methods for analysis.
For cardiovascular events, we considered all components of
coronary events, stroke, cardiac death, or peripheral vascular
disease events, when available from the articles, irrespective
of whether the article included all or some of them.

**Self-quality assessment**

We used the Quality of Reporting of Meta-Analyses
(QUOROM) guidelines to perform the self-quality assessment
of the present work. This file can be located in the manuscript
(Supplementary Table 1).

**Results**

The search for clinical trials and randomized controlled trials
resulted in 3246 articles, of which 332 were found pertinent.
The search for reviews and meta-analysis in omega-3 resulted
in 691 articles, of which 42 were found pertinent. The evalu-
atation of the references of these articles led to the inclusion
of 120 additional references. A total of 452 articles passed
the first evaluation stage on pertinence. Further evaluation
of these articles, submission to inclusion and exclusion criteria
and to the Jadad Scale led to the final number of 21 articles
that are included in the analysis(8–28). This is illustrated as a
flow-chart in Fig. 2.

(A1) **Effects on cardiovascular events**

Cardiovascular events were reported in 14 of the selected
studies, involving 45 285 participants. Cardiovascular events
were lower in the omega-3 group, with 3902 events in
22 669 participants in the omega-3 arm and 4102 events in
22 616 participants in the control group (OR 0.90; [0.85–
0.96]; Z = 3.28, p = 0.001 (Fig. 3). We found medium hetero-
geneity in this group (Chi² = 27.77; I² = 53%). Two studies,
Burr 2003 and Nodari 2011, caused the largest part of the het-
erogeneity, accounting for 29% and 14% of the I² index,
respectively. Furthermore, excluding these 2 studies resulted
in an I² = 0%. 

acid OR DHA OR docosapentaenoic acid OR DPA OR fish oil
OR n-3 fatty acids OR long chain fatty acids OR oily fish OR
fish oil with those for cardiovascular disease (Cardiovascular
OR coronary OR stroke OR peripheral limb disease OR per-
ipheral artery disease OR heart OR heart failure OR preven-
tion). We set a time limit for reviews and meta-analysis
articles (published after January 1st, 2000).
Coronary events were reported in 12 studies, from a total of 41,560 patients. These studies reported a total of 889 coronary events (in 20,792 persons) in the omega-3 group and 1066 events in the control group (in 20,768). These numbers resulted in an OR of 0.82 (0.75–0.90), $Z = 4.17$; $p < 1 \times 10^{-4}$ (Fig. 6). There was no heterogeneity in the results of these 11 studies ($\chi^2 = 8.71; p = 0.65; I^2 = 0\%$).

(A2) Effects on total mortality

Seventeen studies described at least one death and reported total mortality (50,468 participants). Pooled total mortality of all studies reported 2205 deaths in 25,288 participants in the omega-3 group and 2283 deaths in 25,180 participants in the control group, resulting in an OR of 0.91 indicating a lower cardiac death in the omega-3 group (CI: 0.83–0.99; $Z$ for overall effect $1.45, p = 0.15$) (Table 2). There was no evidence of significant heterogeneity of results ($\chi^2 = 2.13, p = 0.14$; $I^2 = 28\%$). Again, the Burr 2003 study showed a divergence from this study. Furthermore, the methodology of the statistical approximation made it impossible to compare directly the effects of marine omega-3 versus placebo, when ALA is excluded from the analysis.

(A3) Effects on cardiac death

Of the 21 articles included in the present review, 13 reported cardiac deaths, of a total of 46,737 participants. The number of cardiac deaths reported was 1108 in 23,499 persons in the omega-3 group and 1198 in 23,328 in the control group. This yielded an OR of 0.91 indicating a lower cardiac death in the omega-3 group (CI: 0.83–0.99; $Z$ for overall effect $1.45, p = 0.15$) (Fig. 5). Evidence of heterogeneity was not found ($\chi^2 = 17.62, p = 0.13$). $I^2$ index ($32\%$) was mainly influenced by the GISSI-Prevenzione 1999 (15\%), and the Burr 2003 (32\%) studies.

(A4) Coronary events

Cardiovascular Events (fatal and non-fatal, involving coronary, cardiac, stroke, peripheral artery disease events). M-H: Mantel-Haenszel. Fixed: Fixed effects. CI: Confidence Interval.
Omega-3 and cardiovascular disease

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>M-H, fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf 1994</td>
<td>0 275</td>
<td>2 273</td>
<td>0·2%</td>
<td>0·20 [0·01, 1·47]</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>Sacks 1995</td>
<td>0 41</td>
<td>1 39</td>
<td>0·1%</td>
<td>0·31 [0·01, 7·82]</td>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>Eristland 1996</td>
<td>8 317</td>
<td>6 293</td>
<td>0·3%</td>
<td>1·24 [0·42, 3·61]</td>
<td>1996</td>
<td></td>
</tr>
<tr>
<td>Leng 1998</td>
<td>3 60</td>
<td>3 60</td>
<td>0·1%</td>
<td>1·00 [0·19, 5·16]</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>GISSI-prevenzione 1999</td>
<td>472 5666</td>
<td>545 5668</td>
<td>26·2%</td>
<td>0·85 [0·75, 0·97]</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>Johansen 1999</td>
<td>1 250</td>
<td>3 250</td>
<td>0·2%</td>
<td>0·33 [0·03, 3·20]</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>Von Schacky 1999</td>
<td>1 112</td>
<td>2 111</td>
<td>0·1%</td>
<td>0·49 [0·04, 5·49]</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>Nilsen 2001</td>
<td>11 150</td>
<td>11 150</td>
<td>0·5%</td>
<td>1·00 [0·42, 2·38]</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>Burr 2003</td>
<td>283 1571</td>
<td>242 1543</td>
<td>10·5%</td>
<td>1·18 [0·98, 1·43]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Leaf 2005</td>
<td>13 200</td>
<td>12 202</td>
<td>0·6%</td>
<td>1·10 [0·49, 2·47]</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Raitt 2005</td>
<td>4 100</td>
<td>10 100</td>
<td>0·5%</td>
<td>0·38 [0·11, 1·24]</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Brouwer 2006</td>
<td>8 273</td>
<td>14 273</td>
<td>0·7%</td>
<td>0·56 [0·23, 1·35]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Yokoyama 2007</td>
<td>286 9326</td>
<td>265 9319</td>
<td>13·5%</td>
<td>1·08 [0·91, 1·28]</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>GISSI-HF 2008</td>
<td>955 3494</td>
<td>1014 3481</td>
<td>38·8%</td>
<td>0·92 [0·82, 1·02]</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>Rouch 2010</td>
<td>88 1919</td>
<td>70 1885</td>
<td>3·5%</td>
<td>1·25 [0·90, 1·72]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Galan 2010</td>
<td>58 1253</td>
<td>59 1248</td>
<td>3·0%</td>
<td>0·98 [0·67, 1·42]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Einvik 2010</td>
<td>14 281</td>
<td>24 282</td>
<td>1·2%</td>
<td>0·56 [0·29, 1·11]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>25288</td>
<td>25180</td>
<td>100·0%</td>
<td>0·95 [0·89, 1·02]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>2205</td>
<td>2283</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 22·17, df = 16 (P = 0·14); I² = 28%

Test for overall effect: Z = 1·45 (P = 0·15)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>M-H, fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf 1994</td>
<td>0 275</td>
<td>2 273</td>
<td>0·2%</td>
<td>0·20 [0·01, 1·47]</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>Sacks 1995</td>
<td>0 41</td>
<td>1 39</td>
<td>0·1%</td>
<td>0·31 [0·01, 7·82]</td>
<td>1995</td>
<td></td>
</tr>
<tr>
<td>GISSI-prevenzione 1999</td>
<td>228 5666</td>
<td>292 5668</td>
<td>26·5%</td>
<td>0·77 [0·65, 0·92]</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>Von Schacky 1999</td>
<td>0 112</td>
<td>1 111</td>
<td>0·1%</td>
<td>0·33 [0·01, 8·12]</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>Nilsen 2001</td>
<td>8 150</td>
<td>8 150</td>
<td>0·7%</td>
<td>1·00 [0·37, 2·74]</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>Burr 2003</td>
<td>180 1571</td>
<td>139 1543</td>
<td>11·8%</td>
<td>1·31 [0·10, 1·66]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Leaf 2005</td>
<td>9 200</td>
<td>9 202</td>
<td>0·8%</td>
<td>1·01 [0·39, 2·60]</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Raitt 2005</td>
<td>2 100</td>
<td>5 100</td>
<td>0·5%</td>
<td>0·39 [0·07, 2·06]</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Brouwer 2006</td>
<td>6 273</td>
<td>23 273</td>
<td>1·2%</td>
<td>0·45 [0·17, 1·20]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Yokoyama 2007</td>
<td>29 9326</td>
<td>31 9319</td>
<td>2·9%</td>
<td>0·93 [0·56, 1·55]</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>GISSI-HF 2008</td>
<td>613 3494</td>
<td>661 3481</td>
<td>51·7%</td>
<td>0·91 [0·80, 1·03]</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>Einvik 2010</td>
<td>5 282</td>
<td>7 281</td>
<td>0·7%</td>
<td>0·71 [0·22, 2·25]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Rauch 2010</td>
<td>28 1919</td>
<td>29 1885</td>
<td>2·7%</td>
<td>0·95 [0·56, 1·60]</td>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>23409</td>
<td>23328</td>
<td>100·0%</td>
<td>0·91 [0·83, 0·99]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>1108</td>
<td>1198</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 17·62, df = 12 (P = 0·013); I² = 32%

Test for overall effect: Z = 2·13 (P = 0·03)

---

Most of the studies analyzed in the present work showed an intriguing uniformity in the direction of their results. The divergent results of one study (Burr et al, 2003) (19) are particularly interesting, as they served as a mirror image for nearly all the outcomes. In fact, all the outcomes of all the studies showed a lower rate of inter-assay heterogeneity I² (<25%), when this study was excluded. Actually, we performed an alternative examination of the results excluding this study, and as well as increasing all the significant findings on cardiovascular events, cardiac death and coronary events, we found a significant change in the total mortality outcome, by lowering the OR to 0·93, 0·87–0·99, Z = 2·18; p = 0·03. It is not easy to work out the explanation for this fact. Some authors have recently reported methodological issues during this study (30–33), such as a transient cessation of the study for a year due to lack of funds, or the fact that participants were not uniformly randomized to omega-3 supplements, and that these were only given to the participants who entered...
the study after a one-year break, which could have created a bias. Some of the authors who recently conducted meta-analyses even excluded the Burr study\(^\text{33,30,32}\). We agree that such issues place limitations on the article, but do not go as far as to discredit it: hence, we have included it. We excluded just one study on methodological grounds, on the light of previous reports\(^\text{34–36}\).

All the results coming from reviews and meta-analyses (and so the ones coming from this work) have to be accepted with caution, due to the fact that the number of studies included are hardly ever designed with the same type of patients, under the same conditions, or with the same intervention. The present study offers results from studies coming from different sets of patients (primary, secondary prevention, spanning over a large range of ages, some of them only accepting men, others only involving persons about to undergo revascularization...), and with remarkable differences in the treatment doses (ranging from 0·3 to 6·9 g) (Table 1). Thus, pooling all the participants together may make it difficult to discriminate effects in subgroups. Furthermore, the size of the study is a critical factor when evaluating the results of a systematic review or the article, but do not go as far as to discredit it: hence, we have included it. We excluded just one study on methodological grounds, on the light of previous reports\(^\text{34–36}\).

Fig. 6. Coronary events (fatal and non-fatal). M-H: Mantel-Haenszel. Fixed: Fixed effects. CI: Confidence Interval.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Odds ratio</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Total Weight M-H, fixed, 95% CI Year</td>
<td>M-H, fixed, 95% CI</td>
</tr>
<tr>
<td>Nye 1990</td>
<td>9</td>
<td>36</td>
<td>16</td>
<td>37</td>
</tr>
<tr>
<td>Sacks 1995</td>
<td>7</td>
<td>41</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>Leng 1998</td>
<td>10</td>
<td>60</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>GISSI-prevenzione 1999</td>
<td>424</td>
<td>5666</td>
<td>485</td>
<td>5668</td>
</tr>
<tr>
<td>Von Schacky 1999</td>
<td>1</td>
<td>112</td>
<td>4</td>
<td>111</td>
</tr>
<tr>
<td>Nilsen 2001</td>
<td>42</td>
<td>150</td>
<td>36</td>
<td>150</td>
</tr>
<tr>
<td>Raitt 2005</td>
<td>10</td>
<td>100</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>Brouwer 2006</td>
<td>10</td>
<td>273</td>
<td>12</td>
<td>273</td>
</tr>
<tr>
<td>Yokoyama 2007</td>
<td>220</td>
<td>9326</td>
<td>290</td>
<td>9319</td>
</tr>
<tr>
<td>GISSI-HF 2008</td>
<td>107</td>
<td>3494</td>
<td>129</td>
<td>3481</td>
</tr>
<tr>
<td>Galan 2010</td>
<td>49</td>
<td>1253</td>
<td>55</td>
<td>1248</td>
</tr>
<tr>
<td>Einvik 2010</td>
<td>0</td>
<td>281</td>
<td>2</td>
<td>282</td>
</tr>
</tbody>
</table>

Total (95% CI) 20792 20768 100·0% 0·82 [0·75, 0·90]

Total events 889 1066

Heterogeneity: Chi² = 8·71, df = 11 (P = 0·65); I² = 0%
Test for overall effect: Z = 4·17 (P = 0·0001)

<table>
<thead>
<tr>
<th>Event</th>
<th>Experimental</th>
<th>Favour controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>0·1 0·2</td>
<td>0·5 1 2 5 10</td>
</tr>
<tr>
<td>Events</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1. Summary of the events total and total events. The table presents the results of the meta-analysis of the effects of omega-3 in the prevention of coronary events (fatal and non-fatal). The table shows the study year, the number of patients, the number of events, and the odds ratio. The table also presents the heterogeneity test and the test for overall effect.

the positive effects of omega-3 (Table 1). Nevertheless, the other recent studies (from 2007 on) showed a similar trend to the GISSI-prevenzione study, despite including most of the medication currently used.

Another important hypothetical point to be considered when dealing with the effects of a certain nutrient (or a substance that may be ingested, such as omega-3 fatty acids) in health or disease is the possibility that the effects of the ‘controlled’ intake of the nutrient (in this case, omega-3) may be influenced by the background diet, and the ‘uncontrolled’ additional intake made by the participants. Moreover, the average intake of the given nutrient in the different populations studied may also influence the results. The effects of omega-3 in populations where its mean consumption is low may be higher than in those populations where the dietary habits include the use of blue fish as a habitual food. For example, even ‘control’ subjects, randomized to not receive supplements of omega-3 in populations like Japan (where usual diet is up to 15 times higher than in western countries\(^\text{37}\)), probably have good average omega-3 intake, when compared to populations with western dietary models, and, hence, there may be an underestimation of the effects of omega-3 due to the fact that even ‘control’ subjects are receiving a good dose of omega-3 via diet. In this sense, omega-3 supplements for people who have a high dietary omega-3 intake fail to reduce triglycerides or modify other plasma lipids\(^\text{38}\). In contrast, populations with low average omega-3 consumption would be theoretically better able to study the effects of the ‘regulated’ intake of omega-3, given that the consumption in normal subjects would be more sporadic. However, these other models could, on the other hand, influence the results of the quantification of the effects of omega-3. In populations with a very low omega-3 intake, it could occur that even with the supplementation of omega-3 (either by dietary or pharmacological means), omega-3 concentration in plasma would not reach a certain
Table 1. Summary of the articles included in this review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Main outcomes (clinical)</th>
<th>Dosage (g) in total content of capsules (DHA/EPA)*</th>
<th>Duration (months)†</th>
<th>Main Findings</th>
<th>Dietary intervention</th>
<th>Drugs (Percentage of use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Nodari, Trig-giani et al. 2011)(28)</td>
<td>HF</td>
<td>2 (5 g during the 1st month)</td>
<td>12</td>
<td>In patients with heart failure and minimal symptoms, omega-3 supplementation increased left ventricle ejection fraction by 10%, and improved markers of response to exercise and functional class of heart failure. Cardiovascular and heart failure hospitalization were 61% and 80% lower respectively.</td>
<td>Not evident</td>
<td>ACE-1 or ARB: 100%; ALD: 60.2%; Amiodarone: 50%; BB: 100%; Furosemide: 100%; Statins: 15%</td>
</tr>
<tr>
<td>(Rauch, Schiele et al. 2010)(27)</td>
<td>Sudden death</td>
<td>1</td>
<td>12</td>
<td>Survivors of AMI derived no benefits from omega-3 supplementation if given in addition to current guideline-adjusted treatment in sudden cardiac death, total mortality, major adverse cerebro-vascular and cardiovascular events or revascularization.</td>
<td>Not evident</td>
<td>AAS: 95%; ACE-1: 83%; Amiodarone: 1.5%; ARB: 8%; BB: 94%; CCB: 8%; Clopidogrel: 88.0%; Digitalis: 3.5%; Diuretics: 34%; Insulin: 10%; OAC: 11.5%; Statins: 94%;</td>
</tr>
<tr>
<td>(Galan, Kesse-Guyot et al. 2010)(26)</td>
<td>Major cardiovascular events</td>
<td>0.6 g of EPA/DHA</td>
<td>56</td>
<td>In patients with a history of AMI, unstable angina, or ischemic stroke, allocation to omega-3 had no significant effect on major vascular events (including non-fatal myocardial infarction, stroke, or death from cardiovascular disease).</td>
<td>Not evident</td>
<td>AAS: 94%; ACE-1: 53.5%; ARB: 9%; BB: 68%; CCB: 15%; Statins: 86%</td>
</tr>
<tr>
<td>(Einvik, Klemsdal et al. 2010)(25)</td>
<td>Deaths and cardiovascular events</td>
<td>2.4 g of EPA/DHA</td>
<td>36</td>
<td>In patients aged 64–76 years, mostly without cardiovascular disease, multi-adjusted hazard ratios of all-cause mortality and cardiovascular events were 0.53 (0.27–1.04, ( P = 0.063 )) and 0.89 (0.55–1.45, ( P = 0.641 )), respectively.</td>
<td>Diet counseling or not in a 2X2 design§.</td>
<td>Treated hypertension: 28%</td>
</tr>
<tr>
<td>(Gissi, Tavazzi et al. 2008)(24)</td>
<td>Morbidity and mortality</td>
<td>1</td>
<td>47</td>
<td>In patients with chronic heart failure (NYHA class II-IV), omega-3 reduced all-cause mortality ([HR] 0.91 [95.5% CI 0.83–0.998], ( P = 0.041 )), hospitalization and death for cardiovascular reasons (adjusted HR 0.92 [99% CI 0.849–0.999], ( P = 0.009 )), respectively.</td>
<td>Not evident</td>
<td>Treated hyperlipidemia: 20%; AAS: 48%; Other anti-platelet: 10%; ACE-1: 77%; ALD: 39%; Amiodarone: 19.5%; ARB 19%; BB: 65%; CCB: 10%; Digoxin: 37%; Diuretic: 30%; Nitrates: 35%; OAC: 29.5%; Statins: 22.5%</td>
</tr>
<tr>
<td>(Yokoyama, Origasa et al. 2007)(23)</td>
<td>Any major coronary event</td>
<td>1.8 g (Only EPA)</td>
<td>56</td>
<td>Hypercholesterolemic patients showed a 19% relative reduction in major coronary events (( P = 0.011 )) in the omega-3 group (only EPA). Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group (HR 0.76 [0.62–0.95], ( P = 0.014 ) and 0.81 [0.68–0.96], ( P = 0.015 )) respectively. In the subgroup analysis, the reduction in major coronary events was more evident in patients with previous CAD (( P = 0.048 )) than in those without CAD (( P = 0.132 )).</td>
<td>Suitable dietary advice for all patients (not specified).</td>
<td>Antiplalet: 14%; BB: 8.5%; CCB: 30%; Other antihypertensive: 26%; Hypoglycaemic: 12%; Nitrates: 10%; Statins: 98%</td>
</tr>
<tr>
<td>Reference</td>
<td>Main outcomes (clinical)</td>
<td>Dosage (g) in total content of capsules (DHA/EPA)*</td>
<td>Duration (months)†</td>
<td>Main Findings</td>
<td>Dietary intervention</td>
<td>Drugs (Percentage of use)</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------</td>
<td>--------------------------------------------------</td>
<td>--------------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>(Brouwer, Zock et al. 2006)²²</td>
<td>Suitable ICD intervention for VT or VF, or all-cause death.</td>
<td>2</td>
<td>12</td>
<td>In patients with ICD and previously-documented malignant VT or VF, omega-3 failed to show a decrease in the episodes of ICD activation for VF or tachycardia (HR 0·86 [0·64–1·16], P = 0·33)</td>
<td>Not Evident</td>
<td>Amiodarone 20%; BB: 55%; Lipid-lowering:45·5%; Sotalol 6·5%</td>
</tr>
<tr>
<td>(Raitt, Connor et al. 2005)²¹</td>
<td>Time to first episode, and recurrence of ICD treatment for VT/VF.</td>
<td>1·8 g of EPA/DHA</td>
<td>24</td>
<td>In patients with implantable ICD and a recent episode of sustained VT or VF, omega-3 did not show beneficial effect in decreasing ICD therapy. Furthermore, in those patients with VT at entry, omega-3 increased the ICD therapy (HR 1·76 [1·16–2·68], P = 0·007)</td>
<td>NCEP‡</td>
<td>ACE-1: 66%; BB: 73·5%; CCB:11%; Digoxin: 31%; Diuretics:53%; Statins: 47·5%</td>
</tr>
<tr>
<td>(Leaf, Kang et al. 2003)²²</td>
<td>Time to first ICD event for VT or VF or death from any cause</td>
<td>4</td>
<td>12</td>
<td>In patients with ICD, omega-3 showed a trend towards a longer time to the first ICD event (VT or VF) or to death (risk reduction of 28%; P 0·057). This trend became significant when the authors included ICD therapy (risk reduction of 31%, P 0·033).</td>
<td>Dietary Advice, with four areas</td>
<td>:</td>
</tr>
<tr>
<td>(Burr, Ashfield-Watt et al. 2003)²⁰</td>
<td>Total mortality, cardiac death and sudden death.</td>
<td>Up to 3 (not specified)</td>
<td>36–108</td>
<td>In patients with angina, all-cause mortality was not reduced by omega-3, and risk of cardiac death and sudden cardiac death were higher (HR 1·26 [1·00–1·56], P 0·047 and HR 1·54 [1·06- 2·23], P 0·025).</td>
<td>Not evident</td>
<td>AAS: 20·5%; ACE-1: 17%; BB: 20%; Diuretics: 18·5%; Statins: 7%; Warfarin: 4·5%</td>
</tr>
<tr>
<td>(Nilsen, Albrektsen et al. 2001)²⁸</td>
<td>Cardiac events</td>
<td>4</td>
<td>18</td>
<td>In patients recruited in early period after an AMI (4–8 days), omega-3 showed no influence on any cardiac outcomes (cardiac death, resuscitation, recurrent AMI, or unstable angina)</td>
<td>Not evident.</td>
<td>AAS: 69%; ACE-1: 5%; BB: 75%; CCB: 41%; Diuretics: 19%; Lipid-lowering: 25·5%; Nitrates: 50·5%</td>
</tr>
<tr>
<td>(von Schacky, Angerer et al. 1999)²⁷</td>
<td>Angiographic changes</td>
<td>6 (first 3 months)</td>
<td>24</td>
<td>In patients with an angioplasty or by-pass surgery planned or performed in the previous 6 months, allocation to omega-3 induced less progression of atherosclerosis in angiograms in the follow-up (P = 0·041), and a trend towards fewer cardiovascular events (P = 0·10).</td>
<td>All patients were advised to avoid eating cholesterol rich foods; no other dietary advice was given.</td>
<td>ACE-1: 17·5%; Antiplatelet: 91·5%; BB: 7·7%; Diuretics: 50·5%; Statins: 7%; Warfarin: 4·5%</td>
</tr>
<tr>
<td>(Johansen, Brekke et al. 1999)²⁶</td>
<td>Angiographic changes</td>
<td>6</td>
<td>6</td>
<td>In patients undergoing an elective angiography, omega-3 induced no differences in the total restenoses rate of arteries (OR 1·25 [0·87–1·80] P = 0·21), or number of patients who suffered those restenoses (OR 1·05 [0·69– 1·59] P = 0·82).</td>
<td>Not evident.</td>
<td>AAS: 69%; ACE-1: 5%; BB: 75%; CCB: 41%; Nitrates: 71%; Warfarin: 17%; Statins: 13%</td>
</tr>
<tr>
<td>(GISSI-Prevenzione, 1999)²³</td>
<td>Combined endpoint (death, non-fatal AMI, and stroke)</td>
<td>1</td>
<td>54</td>
<td>In patients surviving recent (&lt;3 months) AMI, treatment with omega-3 reduced the primary combined end-point by 10%, total mortality by 14%, and cardiovascular death 17% (all in two-way analysis).</td>
<td>Not evident.</td>
<td>ACE-1: 47%; Anti-platelets: 92%; BB:44%; Lipid-lowering: 5%</td>
</tr>
<tr>
<td>Reference</td>
<td>Main outcomes (clinical)</td>
<td>Dosage (g) in total content of capsules (DHA/EPA)*</td>
<td>Duration (months)†</td>
<td>Main Findings</td>
<td>Dietary intervention</td>
<td>Drugs (Percentage of use)</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------------</td>
<td>---------------------------------------------------</td>
<td>-------------------</td>
<td>---------------</td>
<td>----------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>(Leng, Taylor et al. 1999)(73)</td>
<td>Indicators of lower limb disease</td>
<td>0.32 g (EPA + Gammalinolenic)</td>
<td>24</td>
<td>In patients with intermittent claudication, omega-3 and gammalinolenic acid caused no effects on lower limb disease, and less non-fatal cardiovascular events (non-significant).</td>
<td>Not evident</td>
<td>AAS: 43.5%</td>
</tr>
<tr>
<td>(Eritsland, Arnesen et al. 1996)(13)</td>
<td>Angiographic changes (by-pass graft patency)</td>
<td>4</td>
<td>12</td>
<td>In patients undergoing coronary by-pass, graft patency after 1-year was higher (OR 0.77, [0.60–0.99], ( P = 0.034 )) in the omega-3 group, and multiple vein graft occlusion was less frequent (OR 0.72, [0.51–1.01], ( P = 0.05 ))</td>
<td>Not evident. Not provided</td>
<td>Not provided</td>
</tr>
<tr>
<td>(Sacks, Stone et al. 1995)(12)</td>
<td>Angiographic changes</td>
<td>6</td>
<td>28</td>
<td>In patients with angiographically evidenced coronary disease, omega-3 supplementation did not change diameter of coronary arteries or increase of percent stenosis.</td>
<td>NCEP‡. ACE-I: 10.5%; Antiplatelets: 95%; BB: 54.5%; CCB: 47.5%; Nitrates: 33.5%; OAD: 10%</td>
<td></td>
</tr>
<tr>
<td>(Leaf, Jorgensen et al. 1994)(11)</td>
<td>Angiographic changes (restenosis after angioplasty)</td>
<td>10</td>
<td>6</td>
<td>No effect on restenosis rate</td>
<td>NCEP‡</td>
<td>Not provided</td>
</tr>
<tr>
<td>(Bairati, Roy et al. 1992)(10)</td>
<td>Angiographic changes (restenosis after angioplasty)</td>
<td>15 capsules, 4.5 g</td>
<td>6</td>
<td>In patients undergoing a first pre-cutaneous angioplasty, omega-3 group suffered less restenoses (around 20 %, ( P = 0.03 ))</td>
<td>Not evident</td>
<td>Not provided</td>
</tr>
<tr>
<td>(Nye, Ablett et al. 1990)(9)</td>
<td>Angiographic changes (restenosis after angioplasty)</td>
<td>12 capsules, 2.16 g</td>
<td>12</td>
<td>Reduced restenoses versus placebo (11 versus 30 %) and not different from aspirin/dipyridamole. Non-significant decrease in angina episodes</td>
<td>Not evident</td>
<td>Not provided</td>
</tr>
<tr>
<td>(Dehmer, Popma et al. 1988)(8)</td>
<td>Angiographic changes (restenosis after angioplasty)</td>
<td>3.2 g of EPA/DHA</td>
<td>6</td>
<td>Lower early vessel restenosis (3–4 months after angioplasty, 20 % lower). Restenosis per patient was also lower (30 % lower, in the treatment group (46 versus 19 percent).</td>
<td>Not evident</td>
<td>Not provided</td>
</tr>
</tbody>
</table>

Table 1: Main Outcomes, doses, follow-up and main results of the articles included in this review.

*Approx content in EPA/DHA is 0.80 g for each 1 g of capsule content. Where there are notable differences to this fact in the present list, the number of capsules and/or total omega-3 amount is shown.
†Total months, or average mean follow-up when available. Drugs appearing in last column are grouped as they appear in the original reports.
‡All patients were advised to follow a National Cholesterol Education Program Step I diet.
§Diet counseling was aimed at increasing the use of vegetable oils and margarines, vegetables, fruit and fish, and to decrease the use of meat and fat from animal sources. Special oil and margarines containing rapeseed were provided for these participants. 1) To eat at least two portions of oily fish each week, or to take up to 3 g of fish oil (Maxepa) as a partial or total substitute. 2) To eat four to five portions of fruit and vegetables (apart from potatoes) and drink at least one glass of natural orange juice daily, and also increase the intake of oats, so as to obtain a higher intake of vitamin C and at least 8 g of soluble fibre from all sources every day. 3) A combination of both these forms of advice. 4) ‘Sensible eating’ non-specific advice that did not include either of the above interventions. AAS: acetylsalicylic acid. ACE-I: Angiotensin-converting enzyme inhibitor. ARB: Angiotensin II receptor blocker. ALD: aldosterone receptor blocker. AMI: Acute myocardial infarction. BB: beta-blocker. CCB: Calcium channel blockers ICD: implantable cardioverter-defibrillator. OAC: Oral Anticoagulants. T1AA: Type 1 antiarrhythmic agents; VT: ventricular tachycardia; VF: ventricular fibrillation.
Another possible concern when evaluating this particular topic is the fact that the generalized opinion that omega-3 is good for health (and in particular cardiovascular disease) may be influencing the intake of omega-3 (in the form of fish) in the general population, and, more accurately, in those persons that suffer from coronary or other cardiovascular disease. This way, even ‘control’ subjects in randomized controlled studies may have a higher fish consumption than matched healthy persons in their respective populations, and subsequently, a lower difference between the ‘active’ and the ‘placebo’ group would show that even the ‘placebo’ group are receiving (at least partially) the beneficial effects of their intake of fish.

Adherence may be an important factor when analyzing the results, and, in modern studies, persons at secondary prevention receive a large number of medications, especially in the immediate period following the cardiac event. For example, in the OMEGA trial(27), which failed to show any effect of 1 g/d of omega-3 in clinical outcomes, more than the 80% of the patients were taking over 5 different drugs a day, apart from the omega capsules. In a recent sub-study from the JELIS study, adherence was an important determinant of outcomes(39). The rate of adherence was in itself a determinant of the clinical outcomes, even within the treatment arm, and the poor responders had an 80% possibility of receiving the omega-3 pills. Nevertheless, the OMEGA investigators reported a compliance of 70% or more in 93% of the omega-3 group. Regarding this last study, it is also worth noting also that data from the randomization table shown in the article allow us to infer an OR for the combined risk of stroke, previous AMI, previous revascularization, previous by-pass, or moderate (35%–44%) and severe (<35%) reduction of the ejection fraction of 1·12 (1·04–1·20) for the active treatment (omega-3) versus control. In other words, the patients allocated to omega-3 were persons at higher risk (12%) for the combined items of these conditions(27), which may have influenced the ‘negative’ results.

When evaluating the effects of omega-3 fatty acids on clinical outcomes, we are very limited by the time of exposure, the statistical power and the dosage used in the studies. In fact, most of the studies ‘designed’ to discriminate clinical endpoints in a short time (less than six months) fail to find differences - probably because the effects would not become evident until much later. In addition, some of the studies used doses lower than 0·5 g EPA/DHA, which may not allow the trigger plasma concentration required for omega-3 effects to be reached. In other words, some of the beneficial effects of omega-3 may require a prolonged period (up to years) at a certain dose. It has been suggested that although antithrombosis effects may appear with low doses and a low time of exposure (weeks), others, like blood pressure regulation, lowering of triglycerides or lowering of heart rate, could take anything up to a few years(40). Another important factor to be pointed is that some of recent studies calculated their sample size according to expected event rates that were not achieved. For example, in the recent OMEGA trial investigators had a statistical power of 19% to detect differences of risk reduction of 25%. As the risk reduction shown in the omega-3 intake for the clinical outcomes covered in the present study ranges from 5–18%, the probability of this study discriminating such differences was extremely low(27).

As an example of the possible infra-treatment and/or low follow-up, in the GISSI-HF trial, allocation to marine omega-3 (1 g/d) required a follow-up of at least 3–9 years to find differences in total mortality or cardiovascular events(24). In our opinion, only the evaluation of clinical events from long-term exposure to omega-3 fatty acids (up to ten years) with amounts of at least 1 g EPA/DHA would answer this question.

Another issue to take into account when evaluating the apparent disparity of results between studies is population genetics. It is true that genetic background plays an important role in many cardiovascular risk factors, like lipid metabolism, both in fasting and postprandial states(41,42). It is precisely in the modulation of the lipid profile caused by the intake of omega-3 that leads some authors to justify the favorable effects of these products. Recently, Pishva et al showed how a mutation in the FABP gene may account for up to 70% of the effect of the omega-3 fatty acids on triglyceride levels(35). Furthermore, Olano-Martin found that the carriers of another gene mutation at the ApoE locus show an increase in LDL levels when exposed to a high DHA intake(43). This gene-diet interaction was also previously published by Caslake(35). Thus, a different prevalence of gene variations in the populations submitted to each study may lead to different results when evaluating outcomes related to the lipid effects of omega-3.

Although this review is limited to cardiovascular events in randomized controlled trials and clinical trials, we also wanted to remind the reader that many reviews and meta-analyses have included evidence on the efficacy of omega-3 coming from observational and cohort studies, and most of them report a much closer inverse relationship between omega-3 consumption (whether from dietary intake or in the form of supplements) and cardiovascular disease(3,4,5). Thus, a different prevalence of gene variations in the populations submitted to each study may lead to different results when evaluating outcomes related to the lipid effects of omega-3.

The exact mechanisms by which omega-3 performs its functions are still in debate, but the main mechanisms proposed are plaque stabilization(47), lipid profile(48), anti-inflammatory(49), blood pressure(50), heart rate(24,51), or anti-arrhythmic properties(20,52,53). It is precisely on this last effect where major controversy exists today. Initial data from the GISSI-Prevenzione found that most of the decrease in mortality associated with the intake of omega-3 could be due to a decrease in the frequency of sudden death, which leads to the theory that these fatty acids could have anti-arrhythmic properties(15). Nevertheless, the evolution of the study on this topic has shed more controversy than light on
the issue. Although it seems, in the view of some observational and cohort studies, that omega-3 may have the effect of lowering the appearance of atrial fibrillation, especially in the type linked to atrial remodelling associated with age\(^{52}\) (but not in the type associated with cardiac surgery)\(^{54}\), the impact of omega-3 in ventricular arrhythmias is much more debatable. Both pro- and anti-arrhythmic effects of these fatty acids have been reported\(^{20,21,22,55}\) and, perhaps, both really exist. From the different in vitro and in vivo studies, it has been established that omega-3 shortens the action's potential duration and slows down impulse conduction\(^{56,57}\). These actions may reduce the appearance of a triggered activity and subsequent ventricular fibrillation to those usually present in the recent post-infarct state, and, on the other hand, facilitate the appearance of re-entry induced ventricular fibrillation, such as those provoked by other clinical or anatomical causes\(^{55}\).

Regarding the safety of using omega-3, a recent work revisited the incidence of side effects. The only adverse effect that reached statistical significance were gastrointestinal side effects (mainly nausea)\(^{69}\), which occur more frequently at 4 g/d or higher doses, in up to 20% of the patients (or 4% of the patients below 3 g/d)\(^{58}\), which may be accompanied by a fishy taste when belching and may be minimized by taking the supplements with meals or freezing the capsule\(^{59}\). The most severe potential adverse effect studied regarding omega-3 is the potential risk of bleeding, by their effects on platelet metabolism\(^{60,61}\). However, studies which evaluated the safety of using omega-3 up to 4 g/d in takers of anti-platelets and anticoagulants, reported no increased risk on minor or major bleeding events\(^{62,63}\) which has been also confirmed in a recent meta-analysis\(^{65}\). Another potential side effect of the consumption of omega-3 from a dietary source (fish) is the mercury intake that may be involved, especially in big fishes (blue fin tuna, shark, tilefish, swordfish, or king mackerel). Although mercury intake has been related to cardiovascular disease, this relationship is still not yet clearly proven, especially in the amounts that can be derived from eating fish, and to date, the net health benefits of overall fish consumption in adults are clear (for a recent review, please see\(^{64}\)).

In vitro and animal studies suggest that PUFA are more prone to become oxidized than other sources of fatty acids, such as MUFA\(^{65}\). Furthermore, it has been shown that diets rich in omega-3 fatty acids cause an increased susceptibility of lipids to oxidation\(^{66}\). Nevertheless, other studies have not found such results\(^{68–70}\), and a recent study did not find any differences in the different markers of oxidative stress in over 400 patients with metabolic syndrome who consumed four dietary models for 12 weeks, one of which enriched in 1·24 g/d of long chain omega-3 fatty acids\(^{71}\). In conclusion, although omega-3 fatty acids have been shown to increase the susceptibility to oxidation of circulating lipids, studies have not proved that they are linked to an increase in markers of oxidative stress. Further studies are needed to clarify this question.

In conclusion, we have reviewed the effects of marine omega-3 fatty acids on cardiovascular events from randomized controlled trials and clinical trials. The accumulated evidence, as of January, 2012, indicates that marine omega-3, when administered as food or in supplements for at least 6 months, reduces cardiovascular events by 10%, cardiac death by 9% and coronary events by 18%, while showing a trend for a lower total mortality (5%, \(p = 0·13\)). These results are based in the evaluation of studies that included mainly persons with high cardiovascular risk, and in studies which are highly heterogenic in the dose administered, although there is no evidence of dose-dependent protection. Our results, along with the existing evidence on the myriad of physiological effects of omega-3 on human health (coagulation, heart rate, heart rhythm, blood lipids, etc), reinforce the AHA recommendations for the intake of omega-3 in the prevention of cardiovascular disease, especially in persons with high cardiovascular risk and secondary prevention.

**Acknowledgements**

The authors’ responsibilities were as follows: J. D.-L. and P. P.-M. searched the literature, were involved in the conception and design of the study, performed the statistical analysis and drafted the manuscript. J. L.-M. and F. P.-J. supervised the study and provided valuable advice; F. P.-J. also helped search the literature, providing opinions on the pertinence of the articles when there were discrepancies between J. D.-L. and P. P.-M.; all the authors contributed to the interpretation of data, critical review and revision of the manuscript. This work was supported partly by public funds: research grants from the Spanish Ministry of Science and Innovation (AGL 2004-07907, AGL2006-01979, and AGL2009-12270 to J. L.-M., SAF07-62005 to F. P.-J. and FIS P10/01041 to P. P.-M., P110/02412 to F. P.-J.; Consejería de Economía, Innovación y Ciencia, Proyectos de Investigación de Excelencia, Junta de Andalucía (P06-CTS-01425 to J. L.-M., CTS5015 and AGR922 to F. P.-J.; Consejería de Salud, Junta de Andalucía (06/128, 07/43, and PI0193/09 to J L-M, 06/129 to F. P.-J., 0118/08 to F. F-J, PI-0252/09 to J. D.-L., and PI-0058/10 to P. P.-M.); Fondo Europeo de Desarrollo Regional (FEDER). The CIBE-ROBIN is an initiative of the Instituto de Salud Carlos III, Madrid, Spain. The authors report no conflicts of interest.

**References**