IADSA REVIEW OF THE WHO NUGAG REPORT AND RECENT SCIENTIFIC EVIDENCE ON OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE (CHD) RISK AND IMPLICATIONS FOR THE ESTABLISHMENT OF A NUTRIENT REFERENCE VALUE FOR NON-COMMUNICABLE DISEASE (NRV-NCD) FOR EPA AND DHA LONG CHAIN OMEGA-3 FATTY ACIDS BY THE CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECIAL DIETARY USES (CCNFSDU)

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1. Background

At the meeting of the CCNFSDU in November 2015, the co-chairs Russian and Chile put forward a proposal to establish an NRV-NCD of 250 mg/day for EPA + DHA for an association with reduced risk of CHD mortality/fatal CHD events. In December 2016, the CCNFSDU decided to postpone the discussions because of the conflicting evidence and divergent views expressed by delegations and observers. Because of these differences in opinion, the CCNFSDU decided to re-establish the Electronic Working Group (eWG) and continue the discussions in 2017 in accordance with the Codex General Principles for Establishing Nutrient Reference Values for the General Population, taking into account also the work of the WHO Nutrition Guidance Expert Advisory Group (NUGAG) and its final report. The two reports on the NUGAG systematic reviews of RCTs and prospective cohort studies were made available by the eWG in early September 2017 and are summarised in Section 2 and 3 below.

Most importantly for the eWG discussions at the CCNFSDU meeting in December 2017, the NUGAG systematic review of RCTs (pp. 48–54) is dedicated to CHD mortality. The overall statistical analysis of the NUGAG meta-analysis, taking into account moderate to high risk of bias, resulted in the conclusion that there is no effect of long chain n-3 PUFAs on CHD mortality. In contrast, the NUGAG systematic review and meta-analysis of prospective cohort studies for risk of CHD mortality and fatal CHD was associated with statistically significant reductions in risk, ranging from 14 to 26% depending on the levels of intake of total long chain omega-3 PUFAs. In addition, the GRADE assessment of the quality of the epidemiological evidence for the association was assessed as moderate.

In addition to the NUGAG reports of August 2017, there have been a number of other key publications in 2017 that have examined the association between omega-3 fatty acids EPA + DHA and cardiovascular outcomes. The results from these publications are summarised in Section 4.

As noted in the WHO NUGAG report on RCTs, the effect of LCn-3 on CHD deaths appears to depend on assumptions made in the analyses. The results of the scrutiny of individual studies and recent meta-analyses range from findings of no effect through to the observation of a clear and modest effect of EPA + DHA on CHD mortality risk. As a result of the conflicting data

and different interpretations of the totality of the available scientific evidence, there is a high likelihood of any conclusion of the discussion on the establishment of an NRV-NCD being postponed again. Section 5 of this review of the evidence summarises the current IADSA discussion points for the forthcoming CCNFSDU meeting in December 2017.

2. Notes on the abridged version of the WHO NUGAG set of systematic reviews of RCTs on the health effects of omega-3 polyunsaturated fatty acids in adults (Hooper et al. 1st August 2017) relevant to the Codex (CCNFSDU) establishment of an NRV-NCD

The document reports on four systematic reviews of RCTs in adults covering the effects of omega-3 fats on:

i. All-cause mortality
ii. Cardiovascular outcomes, including cardiovascular mortality, cardiovascular events, coronary heart disease and stroke
iii. Lipids and other CVD risk factors
iv. Atrial fibrillation

The aim of the inclusion/exclusion criteria of the studies in the systematic review was that any health effects could be assigned to the omega-3 intervention. Data were collected with respect to participants' baseline risk of CVD, trial duration, intensity of intervention (dietary advice, diet provided, dietary advice plus supplementation), supplementation alone (range of doses), source of omega-3 (plant sources and fish oil supplements), fish consumption, medications used, smoking status etc.

The risk of bias was assessed using the Cochrane risk bias tool. The assessment of risk of bias includes randomisation, allocation concealment, blinding of participants, researchers and outcome assessors, incomplete data, specific and/or combined outcomes, selective outcome reporting, compliance, lack of trial protocol and nature of participant recruitment.

The quality of evidence was rated by means of the GRADE (Grading of Recommendations Assessment, Development and Evolution. Studies by R. B. Singh were omitted by NUGAG because of serious concerns over the veracity of the findings, and studies confounded by other dietary aims (e.g. fruit and vegetable consumption or weight reduction) were also omitted. Risk of bias by funding was not included in the assessment and appears in the table of characteristics instead.

The NUGAG report addressed the following questions:

In Chapter 3: Do dietary or supplemental omega-3 fatty acids alter all-cause mortality?

Summary

- The data were extracted from large numbers of adults enrolled in RCTs over long durations of at least 12 months. The data do not suggest any benefits or harms of omega-3 fats on all-cause mortality.

In Chapter 4. Do dietary or supplemental omega-3 fatty acids alter risk of cardiovascular events, coronary heart disease or stroke (in people with or without existing cardiovascular disease)?

Summary

- There is no evidence that omega-3 fats alter risk of cardiovascular deaths in either primary or secondary prevention of CVD, and there is no suggestion that longer duration or higher doses would be more effective.
- There is no evidence that omega-3 fats alter risk of cardiovascular events in either primary or secondary prevention of CVD.
- Any effect of LC-n3 on CHD deaths appears to depend on assumptions made in the analyses. There was no statistically significant effect of LCn-3 on CHD deaths in the main analysis or in sensitivity analyses. NUGAG concludes that any apparent effect is partly driven by reporting bias and partly by studies at moderate to high risk of bias.
- Although the analysis included over 84,000 participants, 5469 of whom had experienced CHD, the evidence suggesting a small reduction in risk of CHD with LCn-3 intake is not convincing. When NUGAG omitted studies at moderate to high risk of bias, the effect appeared negligible and no longer statistically significant. The overall effect size of all 28 RCTs suggested a 7% reduction in CHD (RR 0.93, 95% CI 0.88–0.97, I2 (see footnote1) 0%, but in the 11 studies at low risk of bias, which included 2222 people experiencing at least one CHD event, there was no clear effect (RR 0.97, 95% CI 0.90–1.05, I2 0%, P=0.51). NUGAG authors suggest that the apparent effect of LCn-3 fats in reducing CHD is due to studies at moderate to high risk of bias only, and is not seen in less biased studies.
- There is no evidence that omega-3 fats reduce the risk of stroke. While there is a suggestion that LCn-3 fats may increase stroke risk in secondary prevention of CVD, no increased risk of stroke is apparent in studies at low risk of bias.
- Myocardial infarction (MI) is reported as a secondary outcome. In 23 trials randomising > 72,000 participants to LCn-3 or a control, 2200 experienced MI. There were no clear effects of LCn-3 fats on MI, whether combined fatal and non-fatal, fatal alone or non-fatal alone.
- For ischaemic and haemorrhagic stroke, the meta-analysis suggests no relationship between any of these secondary outcomes.
- For other cardiovascular outcomes there was no suggestion that omega-3 fats (either LCn-3 or ALA) had any effect on sudden cardiac death, heart failure diagnosis, angina, peripheral vascular events and revascularisations.

1 One measure of heterogeneity is I2, a statistic that indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity. When heterogeneity is substantial, a prediction interval rather than a confidence interval can help have a better sense of the uncertainty around the effect estimate.

In Chapter 5. What are the effects of dietary or supplemental omega-3 fatty acids on sudden cardiac death, heart failure diagnosis, angina, peripheral vascular events and revascularisations?

Summary

- Studies at low risk of bias suggest no effect of omega-3 fats on serum total cholesterol.
- Studies at low risk of bias suggest that LCn-3 fats reduce serum triglycerides, while ALA does not.
- Studies at low risk of bias suggest no effect of omega-3 fats on LDL cholesterol.
- Studies at low risk of bias together with no clear dose effects resulted in NUGAG concluding that there is no effect, or a very small effect only, of LCn-3 on serum HDL.
- The meta-analysis clearly suggested that long term, omega-3 fats from either fish or plant sources had no important effects on blood pressure.

In Chapter 6. Do dietary or supplemental omega-3 fatty acids alter risk of atrial fibrillation (in people with or without existing atrial fibrillation)?

Summary

- Studies at low risk of bias suggest no clear effect of omega-3 fats on new atrial or ventricular fibrillation or ventricular arrhythmia, but if any effect exists, it is likely that LCn-3 fats increase the risk of new atrial fibrillation.
- LCn-3 fats do not appear to reduce new or recurrent arrhythmias.

3. Notes on the WHO NUGAG abridged version of effects of polyunsaturated fatty acid intake and risk of all-cause mortality and cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies (Russell et al. August 2017) relevant to the Codex (CCNFSDU) establishment of an NRV-NCD

The following outcome definitions were used:

All-cause mortality = deaths from any cause during the follow-up period.

Total cardiovascular disease = fatal and non-fatal cardiovascular disease or events that occur during the follow-up period are grouped as a single outcome by the study authors, including acute rheumatic fever, chronic rheumatic heart disease, hypertensive disease, ischaemic heart disease, diseases of pulmonary circulation, cerebrovascular disease, diseases of arteries, arterioles and capillaries, and other diseases of the circulatory system.

Fatal coronary heart disease = death from ischaemic heart disease (IHD) including myocardial infarction, angina pectoris or other forms of chronic IHD.

Non-fatal MI = a sudden or sometimes fatal occurrence of coronary thrombosis, typically resulting in the death of part of the heart muscle, but that does not result in death.

Total CHD = non-fatal MI, angina pectoris and fatal CHD.

Total stroke, fatal stroke, ischaemic stroke and atrial fibrillation were also defined.

For fatal CHD events, there were statistically significant reductions in risk ranging from 14 to 26% with consumption of long chain n-3 PUFAs. The GRADE assessment of the confidence in the estimates of the association was moderate.

Overall, however, the authors downgraded the evidence from the observational studies because of imprecision relating to low sample size, dietary assessment methods, validity of biomarkers, dose range, characterisation of participants in studies, description of cause of death etc. The authors state that observational studies cannot provide causal evidence of an effect of PUFA on health outcomes addressed; they can only describe associations. Poor design, execution and interpretation of studies as well as confounding variables limit interpretation of the epidemiological evidence.

4. Summaries of relevant & additional systematic reviews and meta-analyses published in 2017

4.1. Alexander DD, Miller PE, van Elswyk ME et al. A meta-analysis of randomized controlled trials and prospective cohort studies of eicosapentaenoic and docosahexaenoic long-chain omega-3 fatty acids and coronary heart disease risk. Mayo Clin Proc. 2017; 92(1): 15–29.

This systematic literature search was conducted on 18 RCTs and 16 prospective cohort studies examining EPA + DHA from foods or supplements and CHD, including myocardial infarction, sudden cardiac death, coronary death and angina. Dose-response was also evaluated. The authors state that, to their knowledge, this is the most comprehensive quantitative assessment of the relationship between EPA + DHA supplementation and intake and CHD risk to date. Among RCTs, there was a non-statistically significant reduction in CHD risk with EPA + DHA provision. In subgroup analysis of RCTs with at least 1 g/day of EPA + DHA, reduced risks of most coronary outcomes, including any CHD event,; MI, non-fatal MI, coronary death and angina were observed, although most were not statistically significant. The exception was reduction of risk of non-fatal MI (relative risk estimate, 0.71). The authors pointed out the heterogenicity of individual RCTs including prevalence of CHD at baseline, EPA + DHA dosage, follow-up duration, methods of patient selection, baseline intake of EPA + DHA and other sources in the diet. The meta-analyses of data from prospective cohort studies using higher intakes of EPA + DHA resulted in a consistent, statistically significant reduction of risk for any CHD event (RR, 0.82), fatal CHD events (RR, 0.77), sudden cardiac death (RR, 0.53). The direction of association was similar for the large majority of the prospective cohort studies. Cardiovascular benefits were also observed at lower EPA + DHA intakes in studies of longer duration.

Because a diet low in seafood omega-3 fatty acids is reported to be a contributor to heart disease disability-adjusted life years and is considered a dietary risk factor, authoritative bodies recommend intake of EPA + DHA for heart and overall health.

4.2. Maki KC, Palacios OM, Bell M, Toth PP. J Clin Lipidol.2017 Aug 2. doi: 10.1016/j.jacl.2017.07.010. [Epub ahead of print] Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: an updated meta-analysis and review of research gaps.

Whereas observational evidence on LC-OM3 intake and status show consistent benefits for reduction of cardiovascular risk and lower risks for fatal and non-fatal CHD events, results from RCTs have been mixed, with some suggesting benefits and others showing neutral effects. The purpose of this new meta-analysis and review of research is two-fold, namely to explore further the available RCT data regarding LC-OM3 supplementation and risk for cardiac death and to propose testable hypotheses for the mixed results obtained in RCTs.

From comprehensive PubMed and Ovid/MEDLINE literature searches from a total of 1123 titles and abstracts retrieved, 14 publications met the inclusion/exclusion criteria and were included in the meta-analysis. The results were consistent with the hypothesis that supplemental LC-OM3 may be efficacious for reducing cardiac death in high-risk individuals.

The possible explanations for mixed results in RCTs regarding both fatal and non-fatal CHD events relates to dosage. In this present meta-analysis, reduction in risk for cardiac death was numerically larger in studies that used an EPA + DHA dosage > 1 g/day (RR = 0.709). The authors refer to one large RCT completed in Japan in the JELIS trial in 2007, which showed a statistically significant 19% reduction in major coronary event risk with an intervention of 1.8 g/day of EPA, but no significant reduction in cardiac death. Subsequent analysis of the data showed that participants who benefited were those who had the highest background intake of foods containing LC-OM3. Other studies have also indicated that higher levels may be required to observe the physiological beneficial effects. Many RCTs fail to provide baseline and on-treatment biomarkers of LC-OM3 status to measure the change in status during the intervention. The authors list several underlying metabolic pathways through which a higher LC-OM3 intake could reduce risk for fatal and non-fatal cardiac events, e.g. anti-arrhythmic effects, changes in cardiac structure and function, thrombosis, blood pressure, inflammation, lowering of circulating blood triglyceride concentration etc. Interpretation of some RCTs is difficult because of confounding factors such as the use of cardioprotective drugs such as aspirin, other antiplatelet drugs, statins etc.

Overall, these authors conclude that the present meta-analysis shows a modest (8%) but statistically significant benefits of LC-OM3 supplementation on risk for cardiac death.

4.3. Balk EM & Lichtenstein AH. Nutrients Aug 11 2017; 9(8): 865. doi 10.3390/nu 9080865 Omega-3 fatty acids and cardiovascular diseases: summary of the 2016 Agency of Healthcare Research and Quality Evidence Review.

This analysis of the effects of marine oil supplements on intermediate CVD outcomes remains unchanged from a similar review in 2004. In summary, there is high strength of evidence of no significant effect of marine oils (0.3–6 g/day) on systolic or diastolic blood pressure. There is high strength of evidence that marine oils have small effects on LDL cholesterol and HDL cholesterol concentrations and a large dose-dependent effect on triglyceride concentrations. The authors conclude that there is insufficient evidence regarding the effect of, or associations

between, oils high in EPA + DHA and most CVD clinical and intermediate outcomes. There is low strength of evidence of no association between EPA intake and CHD and between EPA biomarkers and atrial fibrillation.

There is high strength of evidence for no effect of marine oils on risk of major adverse cardiovascular events, all-cause death, sudden cardiac death and blood pressure. There is low strength of evidence for no effect of marine oils on risk of CVD death, CHD death, myocardial infarction, stroke etc.

These authors point out a significant limitation of this analysis in that the RCTs evaluate clinical outcomes with people with known CVD, whereas observational studies evaluate only databases of generally healthy populations without known CVD.

5. Overall concluding observations for consideration by IADSA

- In the case of evidence for EPA + DHA and reduction of risk of CHD mortality/fatal CHD events, the epidemiological evidence is convincing/generally accepted and forms the basis of public health recommendations all over the world. The shortcomings of individual RCTs and assumptions made in subsequent systematic reviews and meta-analyses of RCTs, together with the fact that observational studies can only provide evidence of associations and not cause and effect, have resulted, and will continue to result, in discordance between the different sources of scientific evidence.
- The debates within the scientific community as a whole and the CCNFSDU deliberations raise several issues relating to what is meant by "evidence-based nutrition" and the use of randomised controlled trials (RCTs) as the gold standard. The key issues relate to the limitations and relevance of RCTs to chronic disease development in the general healthy population for which an NRV-NCD is targeted, and to the use of the drug trial paradigm in nutritional science.
- There needs to be a much better understanding and appreciation of the role of well designed and executed epidemiological (prospective cohort) studies and their interpretation for use in setting nutrition policy.
- The complicated statistical analyses of meta-analyses and systematic reviews must be undertaken with caution and interpreted in the light of the totality of the available scientific data and weight of evidence.
- Despite the inconsistencies in research findings and some of the observations demonstrating a neutral or no effect of EPA + DHA on CHD mortality, and the divergent views on the strength of the scientific evidence, the following points are still relevant:

    - The epidemiological prospective cohort studies demonstrate consistent associations between exposure and disease with little or no evidence to the contrary. These scientific conclusions are incorporated into three supporting FAO/WHO expert consultations that are regarded as primary sources of evidence by Codex, as well as several RASBs that focused on specific CHD outcomes.
    - The omega-3 fatty acids EPA + DHA are one of the most researched constituents of foods, and the existing evidence forms the scientific basis for public health recommendations.

- The opportunity exists to focus on the totality of the available scientific data and weight of evidence and for the CCNFSDU, as risk managers for labelling purposes, to fill the vacuum in the Codex labelling guidelines and to synthesise the totality of the evidence to help reduce the global burden of chronic disease from CHD and CVD.
- The beneficial cardiovascular effects are based on biologically plausible physiological mechanisms (e.g. blood pressure, platelet function, blood lipids, endothelial function, cardiac rhythm etc).
- Globally, typical intakes of fish and omega-3 long chain polyunsaturated fatty acids (EPA + DHA) are low.
- As well as the totality of the scientific evidence to support the establishment of an NRV-NCD for EPA + DHA for cardiovascular benefits for the general healthy population, the criteria for setting an NRV-NCD for labelling purposes are fulfilled, namely full characterisation, well established methods of analyses, extensive food composition data, validated biomarkers of nutritional status, understanding of quality aspects and comprehensive safety data.

Overall, IADSA continues to support the proposal put forward by the Russian Federation and Chile to establish a quantitative NRV-NCD for EPA + DHA for the general population for labelling purposes.

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