

A fish a day keeps the doctor away?

May 3 2012

Most people, whether healthy or having cardiovascular disease (CVD), would benefit from regular consumption of oily fish, concluded speakers at the EuroPREvent 2012 meeting. While eating whole fish undoubtedly offers the optimum approach for increasing omega-3 intakes in both primary and secondary prevention, delegates heard, supplements have a major role to play in increasing omega-3 intakes for people who do not like fish. The EuroPREvent 2012 meeting, held 3 May to 5 May 2012 in Dublin, Ireland, was organised by the European Association for Cardiovascular Prevention and Rehabilitation (EACPR), a registered branch of the European Society of Cardiology (ESC).

The symposium "A [fish](#) a day keeps the doctor away" centred on the cardiovascular disease (CVD) benefits of the long chain highly unsaturated omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in the flesh of [oily fish](#), such as salmon, mackerel, herring, trout and [sardines](#). In the round table debate speakers attempted to unravel the current confusion where initial studies showed eating fish/taking omega 3 supplements delivered CVD benefits, but more recent studies with supplements failed to reproduce these effects.

"Omega-3 fatty acids are really important to [human health](#), whether you're talking about CVD, brain or [immune health](#). Health professionals have a key role to play in educating the public about the beneficial effects of including fish in their diets," said Philip Calder, a metabolic biochemist and nutritionist from the University of Southampton, UK.

The latest European Guidelines on Cardiovascular Disease Prevention in Clinical Practice, also launched at the EuroPrevent 2012 meeting, recommend that people should eat fish at least twice a week, one meal of which should be oily fish. For people opting for supplements, warned Calder, it is best to take pharmaceutical grade preparations of omega-3 oils since not all over the counter preparations contain the same dose of the fatty acids. "It's important that health professionals give clear guidance around the need for patients to take 1g of omega-3 a day to achieve any beneficial effects.

With over the counter brands containing different concentrations there's a danger people may not be receiving sufficient intakes," said Calder.

Eating oily fish may prove more beneficial than taking capsules of omega-3. "This is because fish contain all sorts of other nutrients like vitamin D, selenium and iodine that may also be beneficial against CVD. And we don't have the final proof that the benefits from eating fish come from the omega-3," said Daan Kromhout, from Wageningen University, The Netherlands. "Fish, it needs to be remembered, don't provide a total panacea against CVD. As well as consuming fish, people need to eat healthy diets, not smoke and be physically active."

Conflicting trials of omega-3

The first association between omega-3 consumption and incidence of CVD was found in epidemiological studies in the late 1970s when Danish investigators Bang and Dyerberg discovered the incidence of myocardial infarction (MI) was ten times higher among the Danish population than Greenland Inuits. "At the time the Greenland Inuits ate diets of whale and seal meat that were exceptionally high in omega-3 fatty acids," said Erik Berg Schmidt, from Aalborg University Hospital, Aarhus, Denmark. "The findings went contrary to the dogma of the time that animal fats were harmful and led to the hypothesis that omega-3

fatty acids reduce vascular disease."

Omega-3 fatty acids are a family of naturally occurring polyunsaturated fatty acids named according to the position of the double bonds within their hydrocarbon chain. Since mammals lack enzymes to insert the double bond in the omega-6 or omega-3 position, they need to obtain these fatty acids from their diets. EPA and DHA enter the food chain through marine phytoplankton and pass through fish.

The initial trials showing a benefit for omega-3 in the secondary prevention of patients with established CVD were:

- The Diet and Reinfarction Trial (DART), 1989, in 2,033 men who had suffered an MI showed a 29% reduction in all-cause mortality among those who received advice to add two fatty fish meals per week (300 g of oily fish) or to take fish oil capsules providing an equivalent intake of marine omega-3 .
- The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI) Prevenzione trial, 1999, which enrolled 11,324 patients within three months of an MI, showed that marine omega-3 fatty acids (885 mg EPA+DHA per day) lowered the risk of the combined primary outcome of death and non-fatal cardiovascular events by 15% .
- The JELIS study, 2007, which involved 18,645 Japanese patients with hypercholesterolaemia, with or without pre-existing coronary artery disease, showed that long-term use of 1.8 g of purified EPA daily lowered the risk of the combined primary outcome of death and non-fatal cardiovascular events by 15% .

However, in 2010, three large trials - Alpha Omega, OMEGA, and SU.FOLOM3 – all failed to confirm the benefits of omega-3 fatty acids supplements on CVD events.

Each of these later studies, said Berg Schmidt, had issues related to the marine omega-3 fatty doses used, the exact mix of EPA and DHA, the lag between when the MI occurred and initiating omega-3 fatty acid treatment, the use of newer invasive and non-invasive strategies, the length of follow-up and sample size, which in some cases was too small to show a beneficial effect.

Fish intake in primary prevention

Following the first epidemiological observations in Greenland Inuits, Kromhout told delegates, prospective cohort studies carried out in European, American, Japanese, and Chinese populations also showed inverse associations between fish consumption and CVD morbidity and mortality.

Recently a Danish cohort study from Aalborg found that when levels of omega-3 fatty acids were measured in an adipose biopsy taken from the buttocks of 57 053 subjects, a negative dose response was found with the risk of acute MI. "But there've been no trials of eating fish in healthy people because you'd need too many participants to reach a conclusion for the trial to be feasible," explained Kromhout.

The only real way to look for benefits in primary prevention, he added, is to investigate the effects on intermediate endpoints. One such study by Matthew Pase, from the NICM Centre for Study of Natural Medicines and Neurocognition, Melbourne, Australia, reviewing data from 10 clinical trials involving 550 participants, found omega-3 fatty acids reduced pulse wave velocity by an average of 33 % and arterial compliance by 48 %.

The mechanism of action of Omega-3 fatty acids

Omega-3 fatty acids, explained Calder, can exert a variety of actions on cell physiology and function. "They're anti-inflammatory and might therefore decrease the inflammatory processes within the vessel wall, which are recognised as major contributors to atherosclerosis," he said.

Indeed, recent studies by Calder and colleagues showed that the incorporation of EPA into advanced plaques was associated with a decreased expression of various matrix metalloproteinases (MMPs), proteins which have been implicated in plaque cap thinning and increased vulnerability to rupture.

Omega-3 fatty acids are also known to have an anti-arrhythmic effect. The presence of omega-3 fatty acids in cardiomyocyte membrane phospholipids decreases electrical excitability and modulates the activity of ion channels (e.g. sodium, potassium and calcium, effects that are claimed to promote electrical stability in the cell and prevent arrhythmias. It is also known that omega-3 [fatty acids](#) are potent triglyceride lowering agents.

One issue that has hindered studies exploring the mechanisms of action of omega-3, added Calder, is that the amounts of EPA and DHA vary between the different commercial preparations of omega-3. "This is important because EPA and DHA don't always have the same actions," he said.

"With investigators using different doses it's been hard to produce consistent effects. To properly unravel the mechanisms we need to adopt a strategic multidisciplinary approach where everyone uses the same dose and relative amounts of EPA and DHA" said Calder.

More information: *EHJ* 2012. [Doi: 10.1093/eurheartj/ehs092](https://doi.org/10.1093/eurheartj/ehs092)

Provided by European Society of Cardiology

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