



Daan Kromhout: 'Just keep on eating fish.'

## 25 YEARS OF STUDYING FISH FATTY ACIDS

# ‘Cardiology has overtaken us’

**Daan Kromhout attracted international publicity with a major study of the effects of fish fatty acids on heart disease. The results were somewhat disappointing. Yet ‘the underlying conclusion is that heart patients in the Netherlands in the past ten years have had very good treatment.’**

TEKST ASTRID SMIT PHOTOGRAPHY ROGIER VELDMAN

**D**aan Kromhout, professor of Public Health Research at Wageningen University (part of Wageningen UR), was the focus of much attention at the end of August, when he announced the long-awaited results of the famous Alpha Omega Trial in *The New England Journal of Medicine*. It was hoped that this large-scale double-blind research on the effects of fish fatty acids in five thousand heart patients would provide definitive proof of the beneficial effects of omega 3 fatty acids from fish on cardiovascular disease. Sadly, that proof was not forthcoming. At least, not across the board. It turned out that only heart patients who also have diabetes benefit from the fish fatty acids. A pity for the research, but not a bad outcome in itself, says Professor Kromhout. ‘Cardiologists have been treating heart patients so well in the last ten years that we can no longer measure any possible effects of omega 3 fatty acids.’

Anyone who talks to Kromhout’s colleagues, hears positive opinions. What emerges is an image of someone who can inspire colleagues and students tremendously, who discovers gold mines where other only see a mess, who works with the utmost dedication on one subject for years and only gives up when there is not a glimmer of hope left. ‘I recognize the last bit of that’,

says Kromhout in his office at the Biotechnion building. ‘Once I’m grabbed by something, I go for it.’ Kromhout has been working on the relation between fish and cardiovascular disease for more than 25 years. It was at the university of Leiden that he first discovered the added value of fish. As a researcher and later as professor of Nutrition and Epidemiology, he devoted his attention to the Zutphen study, a research in which the eating habits and health of around 900 middle-aged men were monitored for years. ‘With this database I could make my dream come true: researching the link between nutrition and health.’

### HALF-JOKING

For a colleague’s farewell symposium, Kromhout looked, half-jokingly, to see whether he could find a link between fish consumption and heart disease in the Zutphen men. And sure enough, those who ate fish once a week lowered their chances of a heart attack by as much as fifty percent compared to the men who never ate fish. ‘A beautiful result’, says Kromhout, who has lost none of his enthusiasm. ‘We first offered the article to *The Lancet*, but they didn’t want it. *The New England Journal of Medicine* did, and it was published in 1985. It was an immediate hit.’ >

## OMEGA 3 FATTY ACIDS FROM FISH

It is not entirely clear why omega 3 fatty acids from fish can be health-promoting. There is a hypothesis though. Daan Kromhout thinks that two mechanisms play a role. With low consumption levels – from one to twenty grams of fatty fish per day – fish fatty acids lower the risk of a serious heart rhythm disturbance. They are absorbed into the membrane of the heart cells, promoting flexibility. The conduction of electrical impulses is improved by this and the chances of developing a serious heart rhythm disturbance – a frequent cause of sudden death – go down. With high consumption levels – one to four hundred grams of fatty fish per day – the omega 3 fatty acids reduce the build-up of fatty deposits in the arteries and cut the risk of thrombosis. The fish fatty acids increase the stability of the plaque that builds up on the artery walls, so that it breaks up less easily. And if this does happen, a blood clot is likely to form.



Four years later, British epidemiologists confirmed the link in an intervention study. Heart patients who were advised to eat fatty fish at least twice a week had a thirty percent smaller risk of dying of a heart attack in the next two years. A similar link was found in the Seven Countries Study, of which the Zutphen study was a part. In Finland, the Netherlands and Italy, the consumption of fatty fish went together with a lower risk of fatal heart disease.

### A GLASS OF WINE

But these are all correlations, not hard evidence. In the British study, the patients knew which group they were in – the one advised to eat fish or the other one. That could have influenced the result. It could be that someone who is advised to eat fish adopts some other new and healthier behaviour as well. And this could mask the effect of the fatty fish. Moreover, the doctors knew too much and could therefore have misinterpreted the medical results. And in the Seven Countries Study, it could have been another factor that caused the lower death rate from heart disease in Finland, the Netherlands and Italy. The glass of white wine that many people enjoy with their fish, for example.

To rule out these confounding factors, Kromhout decided to conduct the Alpha Omega Trial: a double-blind nutritional intervention study in which heart patients did not know which group they were in. He asked Unilever to develop four margarines: one with fish fatty acids (both EPA and DHA), one with alpha-linolenic acid (ALA), a precursor of the omega 3 fatty acids, one with

all three – EPA, DHA and ALA, and one with none of the fatty acids: the placebo. These margarines were given for a period of forty months to almost five thousand patients who had had one heart attack. 'It is the first double-blind nutritional intervention study on omega 3 fatty acids with what we call hard endpoints', says Kromhout. 'We recorded exactly when people went into hospital, what sort of treatment they received and when they died.' The study cost seven million euros, an amount that was only raised after some hard lobbying and thanks to the Dutch heart foundation, the American National Institute of Health, and Unilever, who agreed to deliver the margarine to the patients' doors for three years free of charge.

### NO PROOF

The ten-year project came to an end this year. The blow came when Kromhout looked at the data from the trial at the beginning of April: the main hypothesis – that omega 3 fatty acids from fish lower the risk of cardiovascular disease – had not been proven. There seemed to be no difference between the groups eating the different margarines. 'I was a bit disappointed, yes', laughs Kromhout now. 'Later I came to see it differently. Because after all, the underlying conclusion is very positive. Cardiologists have been giving heart patients such good treatment over the past ten years that we can no longer measure the possible effects of omega 3 fatty acids. Cardiology has overtaken us.'

On the basis of intervention research projects in the nineteen nineties – in which some of the participants

who had had one heart attack were advised to eat fatty fish twice a week – he had reckoned on 360 deaths from heart attacks in the Alpha Omega Trial. But there were only 138. Kromhout: ‘The risk of death from a heart attack went down from the expected 80 percent to 30 percent.’ The reason: Dutch cardiologists have started prescribing more medicines. Ninety percent of the heart patients were taking blood thinners, 85 percent were taking statins – to lower cholesterol – and 98 percent were taking anti-thrombosis drugs such as aspirin. By contrast, the heart patients in the British study in the nineteen eighties were on hardly any medicines. In 1994, research on statins showed how effective these medicines could be in reducing cholesterol. ‘When our research started, cardiologists were starting to prescribe statins a lot. Our trial was actually conducted ten years too late. But, well, we hadn’t raised the funding until then.’

### INTERESTING CORRELATIONS

Although the main hypothesis of the Alpha Omega Trial was not proven, some interesting correlations did come out of it. Diabetics did benefit from the omega 3 fatty acids: in the group eating fish fatty acids, the death rate from heart attacks dropped by fifty percent. And in those taking both the fish fatty acids and alpha-linolenic acid, the number of severe heart rhythm disorders also dropped by fifty percent. However, no hard conclusions can be drawn from these subgroup analyses. ‘In Oxford there is now a big research being done on the relation

‘If you can’t entirely prove your hypothesis, that is just bad luck’

between fish fatty acids and cardiovascular disease in diabetes patients. If those researchers confirm our results, we can still raise the flag, as far as I’m concerned.’

The Alpha Omega Trial is not quite the hoped-for glorious conclusion to 25 years of research on fish fatty acids, Kromhout admits. But he is by no means a disappointed researcher either. ‘I am far too optimistic for that. If you are a true researcher, you test hypotheses you believe in. And if you cannot entirely prove them, that’s just bad luck.’ Kromhout is taking a break from omega 3 fatty acids from fish. For the time being there are no more possibilities for proving that these fatty acids can have a beneficial effect. Other intervention studies are either too expensive or not feasible.

So what should an ordinary mortal do about the advice to eat fish twice a week? Just keep on following it, says Kromhout. The evidence from epidemiological studies that fatty fish can prevent cardiovascular disease is still very strong. ‘There’s a lot more in fish besides fatty acids, too. There are other healthy substances such as vitamin D and selenium, so perhaps it’s about the total package.’ Another glimmer of hope. ■

### DAAN KROMHOUT (60)

Daan Kromhout is professor of Public Health Research at Wageningen University, deputy chairperson of the Health Council in The Hague and part-time professor at the University of Minnesota in Minneapolis in the US. He is also professor at the Royal Dutch Academy of Sciences in Amsterdam. Kromhout has published more than 330 scientific articles, 200 other publications and two books about the Seven Countries Study. His research focuses on cardiovascular diseases, lifestyle, nutrition and healthy aging.

Kromhout’s career began in Wageningen, where he studied human nutrition and obtained his PhD. He then moved to the University of Leiden, where he was professor of Nutrition and Epidemiology from 1984 to 1994. After four years he was also appointed to the National Institute of Public Health and Environment (RIVM). In 1994, Kromhout moved from Leiden to Wageningen. He left the RIVM in 2005, when he was asked to help chair the Health Council. Since then he has combined this role with his job as professor at Wageningen.

