

The Fish Story

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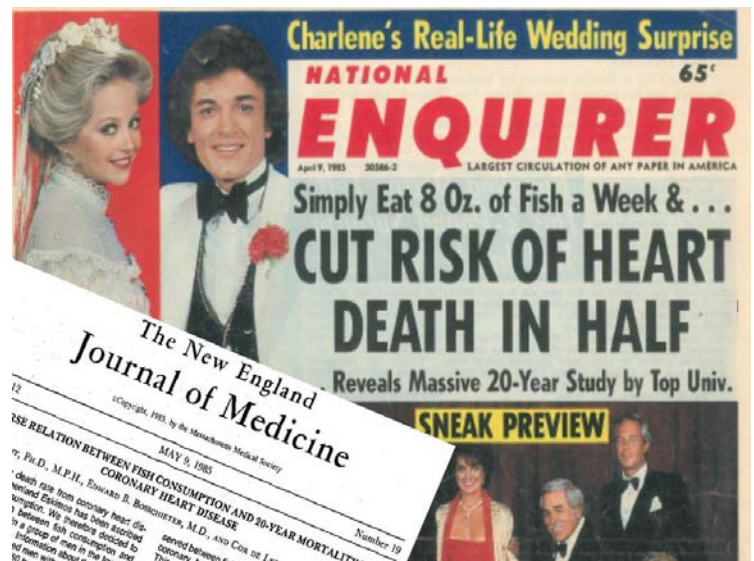
After my PhD at Wageningen University I moved in 1978 to the University of Leiden and became the Principal Investigator of the Zutphen Study, the Dutch contribution to the Seven Countries Study. This Study was initiated and directed by Professor Ancel Keys from the University of Minnesota, Minneapolis. My research at that time was focused on diet, serum cholesterol and coronary heart disease (CHD). I collaborated on this topic with Professor Alexander Arntzenius, Professor of Cardiology, who had a strong interest in preventive cardiology. His major research project at that time was the Leiden Intervention Study, a study on the effect of a healthy diet on progression of atherosclerosis.

In 1982 my colleague Frans Kok, now the chair of the Division of Human Nutrition of Wageningen University and I went to the International Congress of Atherosclerosis in Berlin. During that Congress Professor Arntzenius preached us about the importance of white fish for CHD prevention. When we asked the evidence for this relation he said that the Inuit ate a lot of seafood and had a very low CHD



mortality rate. Two years later Professor Arntzenius called me and told that he would retire in a couple of months and that for his retirement a mini-symposium would take place. Dr. Basil Rifkind from NIH was invited to talk about cholesterol, Professor Arntzenius would give his farewell lecture and I should deal with diet and CHD. I asked whether he had a preferred topic for me but he said that I should do what I like. Then I remembered his seafood story from Berlin and decided to analyse the association between fish consumption and CHD in the Zutphen Study. At the start of the analysis I became very disappointed because the average fish consumption of the middle-aged men in Zutphen was on only 20 grams per day, compared to the 400 gram seafood per day of the Inuit men. In spite of that I decided to continue the analysis and found that the 20-year CHD mortality was more than 50 per cent lower among the men who consumed more than 30 gram of fish per day compared to those who did not eat fish. The conclusion of this analysis was that as little as one or two dishes of fish per week may be protective against CHD.

Together with the internist Edward Bosschieter MD and the statistician Cor de Lezenne Coulander MSc I prepared a paper that was first submitted to the Lancet. The reason that I submitted the paper to the Lancet was a discussion I had had with professor Arntzenius about were to publish his main paper on the Leiden Intervention Study and my fish paper. He had a strong preference for the Lancet so it became the Lancet because of his seniority. But both papers were rejected by the Lancet. As a



joke I suggested to him to submit the two papers to the New England Journal of Medicine and both were accepted. Both papers became highly cited and my fish paper became in 1993 a citation classic of the Institute of Scientific Information and has now been cited more than 1,500 times.

Twenty five year later I published together with my colleagues Dr Marianne Geleijnse and Dr. Erik Giltay the results of the Alpha Omega Trial. In this trial we examined the effect of the marine n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and of the plant-derived alpha-linolenic acid (ALA) on the rate of cardiovascular events among 4,837 patients who had had a myocardial infarction and who were followed for 40 months.

This study showed that an additional amount of 400 mg EPA-DHA per day equivalent to two fish meals per day or 2 gram ALA, equivalent to the recommended intake of this fatty acid per day did not significantly reduce fatal CHD. This negative effect was probably due to the fact that those patients were receiving state-of- the-art antihypertensive, antithrombotic and lipid-modifying therapy. Recent detailed analyses of two subgroups of the trial showed that in post-myocardial infarction patients who also had diabetes and who received an additional dose of EPA-DHA and ALA reduced their risk of ventricular-arrhythmia-related events substantially. The subgroup of patients who did not use statins and who received an additional amount of EPA-DHA and ALA reduced the risk of major cardiovascular events. These results have first to be evaluated in other trials before definitive conclusions can be drawn on the causality of the relation between these fatty acids and major cardiovascular events.

My publication on fish consumption and fatal CHD in the Zutphen Study was the first that suggested that a small amount of fish may be protective against fatal CHD. The results of the Alpha Omega Trial on n-3 fatty acids and major cardiovascular events showed that in state-of- the-art treated post-myocardial infarction patients n-3 fatty acids did not affect future cardiovascular events. These two publications in the New England Journal of Medicine on my fish story were not only important in relation to the fish story at large but also played a major role in shaping my career.