

# Blood Levels of Long-Chain n-3 Fatty Acids and the Risk of Sudden Death

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FROM ABSTRACT

## Background

Experimental data suggest that long-chain n-3 polyunsaturated fatty acids found in fish have antiarrhythmic properties, and a randomized trial suggested that dietary supplements of n-3 fatty acids may reduce the risk of sudden death among survivors of myocardial infarction.

Whether long-chain n-3 fatty acids are also associated with the risk of sudden death in those without a history of cardiovascular disease is unknown.

## Methods

We conducted a prospective, nested case-control analysis among apparently healthy men who were followed for up to 17 years in the Physicians' Health Study.

The fatty-acid composition of previously collected blood was analyzed by gas-liquid chromatography for 94 men in whom sudden death occurred as the first manifestation of cardiovascular disease and for 184 controls matched with them for age and smoking status.

## Results

Base-line blood levels of long-chain n-3 fatty acids were inversely related to the risk of sudden death both before adjustment for potential confound and after such adjustment.

As compared with men whose blood levels of long-chain n-3 fatty acids were in the lowest quartile, the relative risk of sudden death was significantly lower among men with levels in the third quartile (adjusted relative risk, 0.28) **[72% reduced risk]** and the fourth quartile (adjusted relative risk, 0.19) **[81% reduced risk]**.

## Conclusions

The n-3 fatty acids found in fish are strongly associated with a reduced risk of sudden death among men without evidence of prior cardiovascular disease.

## THESE AUTHORS ALSO NOTE:

Fish consumption is associated with reduced risk of sudden death from cardiac causes.

“It is hypothesized that the long-chain n-3 polyunsaturated fatty acids found in fish, primarily eicosapentaenoic acid and docosahexaenoic acid, may be responsible for this association.”

Experimental data indicate that that n-3 fatty acids have antiarrhythmic properties.

Randomized trial testing n-3 fatty acid supplements in survivors of myocardial infarction found a 45% reduction in the risk of sudden death.

This study is a prospective study, and it involves the effects of long-chain n-3 fatty acids in the diet or as supplements among persons without a history of cardiovascular disease.

This is important because persons without a history of cardiovascular disease represent half of all cases of sudden death from cardiac causes.

This study involved 22,071 male physicians, who were 40 - 84 years old in 1982, and had no history of myocardial infarction, stroke, transient ischemic attacks, or cancer. The follow-up period for this group was 17 years.

The blood level of long-chain n-3 fatty acids was significantly correlated with fish intake.

“The mean level of total long-chain n-3 fatty acids was significantly lower among the men who died suddenly than among the controls.”

“The level of long-chain n-3 fatty acids was significantly inversely related to the risk of sudden death in both the analysis adjusted for age and smoking status.”

## DISCUSSION

“In this prospective, nested case-control study of healthy male physicians without evidence of cardiovascular disease at enrollment, the base-line blood level of long-chain n-3 fatty acids was inversely associated with the subsequent risk of sudden death, even after known confounders had been controlled for.”

“As compared with men with levels of long-chain n-3 fatty acids in the lowest quartile, those with levels in the highest quartile had an 81 percent lower risk of sudden death.”

The “data support the hypothesis that long-chain n-3 fatty acids are responsible for the observed inverse association between fish consumption and sudden death.”

In a previous study [Lancet, 1999], men with a history of myocardial infarction who were assigned a fish-oil supplement had a significant 45% reduction in the risk of sudden death, and a significant reduction in total mortality.

“The apparent beneficial effect on the risk of sudden death from cardiac causes in observational studies and randomized trials could be due in part to the antiarrhythmic effects of n-3 fatty acids.” (3 references)

Plausible mechanisms for the antiarrhythmic effects of n-3 fatty acids include:

- (1) Modulation of sodium, potassium, and calcium channels.
- (2) Inhibition of the production of thromboxane.
- (3) Beneficial effects on heart-rate variability.
- (4) Lowering of nonesterified fatty-acids in plasma and cell membranes.  
(Nonesterified fatty acids have multiple proarrhythmic properties).

“In summary, taken together with previous data from observational studies and randomized trials, these prospective data suggest that the long-chain n-3 fatty acids found in fish may reduce the risk of sudden death from cardiac causes, even among men without a history of cardiovascular disease.”

“Because more than 50 percent of all sudden deaths from cardiac causes occur in people with no history of cardiac disease, preventive efforts must address this segment of the population to have a substantial effect on the overall incidence of sudden death from cardiac causes.”

“The intake of n-3 fatty acids by eating more fish or by taking supplements is an intervention that could be applied to this segment of the population at low cost and little risk.”

THIS ARTICLE GENERATED THIS EDITORIAL, IN PART:

## **Fish – Food to Calm the Heart**

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Marine sources of “unsaturated fatty acids are a central element in the diet–heart hypothesis, which emerged in the mid-20th century and has dominated public health discourse in nutrition ever since.”

Marine or fish oils in the diet and their apparent “protective effects against death from cardiovascular disease, the number-one killer in the industrialized world, resulting in 250,000 sudden deaths yearly in the United States.”

This article adds to the growing body of evidence that “eating long-chain n-3 polyunsaturated fatty acids, largely from fish, may provide protection against sudden death from cardiovascular causes.”

N-3 fatty acids may:

- (1) Prevent ventricular arrhythmias and sudden death
- (2) Prevent abnormal lipid metabolism
- (3) Regulate blood-pressure
- (4) Enhance brain and retinal development
- (5) Improve immune modulation
- (6) Improve platelet function and clotting

“Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)—derived largely from marine species, especially fatty fish (salmon, bluefish, mackerel, arctic char, and swordfish), are mainly responsible for the protective effects of this group of substances.”

The protection from sudden death due to cardiac arrhythmias is not the result of the protective action of n-3 fatty acids in blood but rather “the effect of diet on the fatty-acid content of phospholipids in heart-cell membranes in the functionally critical SN2 position.”

“In the event of severe physiological stress, such as that caused by the loss of blood supply to a portion of the heart early in an ischemic attack, the DHA or EPA occupying the SN2 position in phospholipids is released and protects the heart cell locally from participating in the genesis and propagation of ventricular tachycardia, which can result in cardiac arrest and sudden death.”

**[All phospholipids have a 3-carbon glycerol backbone.]**

<b>C--FA</b>	<b>Sn1 =</b>	<b>CH2O - Fatty Acid</b>
<b>C--FA</b>	<b>Sn2 =</b>	<b>CHO - Fatty Acid</b>
<b>C--P</b>	<b>Sn3 =</b>	<b>Ch20 - P - choline or inositol or serine</b>

"This protective effect, which is absent if other fatty acids derived from the diet occupy the SN2 position, depends on the unique ability of these n-3 fatty acids to stabilize all contractile heart cells electrically and thus protect against sudden death from arrhythmias."

"It is both safe and prudent to eat, as recommended by the American Heart Association, at least two servings of fish per week, especially fatty fish, as we strive for an intake of n-3 fatty acids approaching 1 g per day."

"There are also likely to be other beneficial effects of the intake of n-3 fatty acids that are not discussed by Albert et al., including those on blood triglyceride levels, the immune system, the developing central nervous system (by the transmission of fatty acids through breast milk), clotting mechanisms, and blood pressure."

#### KEY POINTS FROM DAN MURPHY

- (1) Half of those who suffer sudden cardiac death have no history of cardiac disease.
- (2) The cause of these deaths is primarily cardiac arrhythmia.
- (3) In apparently healthy men, those with the highest 25% of n-3 fatty acid in their blood had a reduced risk of sudden cardiac death from arrhythmia by 81% as compared to those with the low 25% of blood n-3 fatty acid levels.
- (4) N-3 fatty acids also benefit the vascular system, the immune system, and the brain.
- (5) N-3 fatty acids have antiarrhythmic properties, especially eicosapentaenoic acid and docosahexaenoic acid.