

**Citation:**

Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. *Circulation*. 2005 Jan 18; 111(2): 157-164. Epub 2005 Jan 3.

**PubMed ID:** [15630029](#)

**Study Design:**

Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-administered validated FFQ at multiple time points and development of CHD assessed by biennial health history questionnaire.

**Class:**

B - [Click here](#) for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To investigate the association between intermediate and long chain omega-3 (n-3) and omega-6 (n-6) PUFA intake on the incidence of CHD.

**Inclusion Criteria:**

Professional men free from CHD and participating in the Health Professionals follow-up study.

**Exclusion Criteria:**

Pre-existing CHD or implausible total energy intake (less than 800kcal or more than 4,200kcal per day) on baseline questionnaire.

**Description of Study Protocol:****Recruitment**

Subjects participating in the Health Professionals follow-up study provided the data for this study.

**Design**

A prospective 14-year follow-up (cohort) study assessing lipid intake and controlled for lifestyle and other dietary variables and the incidence of CHD. A self-administered 131-item validated FFQ was used to collect data on fatty acid intake. Intake of nutrients was determined by frequency times the content of a standardized serving size. Nutrient content was determined using the USDA and Harvard University food composition data bases. The FFQ was administered multiple times (at baseline and every four years) and weighted toward the most recent intake. Measures were made until subjects were censored by a diagnosis of angina, coronary artery bypass, hypercholesterolemia, hypertension, diabetes or stroke, which was assumed to alter their dietary intake.

## Statistical Analysis

Cox Proportional Hazards analysis with time varying covariates. Data were censored after the first CVD event, death or last date of follow-up. The alpha was set at  $P=0.05$ . Dichotomous variables were formed from fatty acid intake of n-3 linolenic acid (ALA), n-6 PUFA, and EPA+DHA, using categories of more than median or less than median values. Data were adjusted for age and in the multiple analysis, for lifestyle, BMI, smoking, PA, history of DM, hypertension, hypercholesterolemia, aspirin use, alcohol (EtOH), protein intake, saturated fat, monounsaturated fatty acids, trans-fat and dietary fiber.

## Data Collection Summary:

- *Timing of measurements:* Biennial health and lifestyle habits questionnaire. The FFQ was administered at baseline and every four years afterward.
- *Dietary variables:* MUFA, SF, trans-fat, fiber, cholesterol, protein, ALA and EtOH.
- *Other variables:* Smoking, physical activity, age, aspirin, cholesterol or blood-pressure-lowering medications, diabetes, hypertension, hypercholesterolemia and BMI.

## Dependent Variables

- *Variable One:* Non-fatal MI (review of health history and verification by examination of medical record)
- *Variable Two:* Sudden cardiac death (Death ascertained from relatives, postal authorities, National Death Index. Cause of death was found in death certificate, examination of medical record or autopsy findings.)
- *Variable Three:* Total CHD (review of health history and verification by examination of medical record).

## Independent Variables

n-6 PUFA intake, n-3 DHA and EPA intake, n-3 ALA intake.

## Control Variables

- *Dietary variables:* MUFA, SF, trans-fat, fiber, protein, ALA and EtOH
- *Other confounders:* Smoking, physical activity, age, aspirin use, cholesterol or blood-pressure-lowering medications, diabetes, hypertension, hypercholesterolemia and BMI.

## Description of Actual Data Sample:

- *Initial N:* 51,529 males
- *Attrition (final N):* 45,722 males
- *Age:* 40 to 75 years
- *Other relevant demographics:* Health professionals
- *Location:* US.

## Summary of Results:

		<b>Low EPA + DHA</b>		<b>High EPA + DHA</b>	
		<b>Low n-6</b>	<b>High n-6</b>	<b>Low n-6</b>	<b>High n-6</b>
<b>Sudden Death</b>	<i>Age-adjusted</i>	1.0	0.85 (0.6, 1.2)	0.48 (0.32, 0.71)*	0.69 (0.48, 1.01)
	<i>Multivariate</i>	1.0	0.76 (0.52, 1.1)	0.52 (0.34, 0.79)*	0.60 (0.39, 0.93)*
<b>Non-Fatal MI</b>	<i>Age-adjusted</i>	1.0	1.14 (0.99, 1.32)	1.08 (0.94, 1.25)	1.09 (0.94, 1.27)
	<i>Multivariate</i>	1.0	1.09 (0.93, 1.28)	1.16 (0.99, 1.36)	1.09 (0.91, 1.29)
<b>Total CHD</b>	<i>Age-adjusted</i>	1.0	1.01 (0.90, 1.14)	0.96 (0.86, 1.08)	1.02 (0.91, 1.16)
	<i>Multivariate</i>	1.0	0.97 (0.85, 1.10)	1.05 (0.92, 1.19)	1.02 (0.89, 1.16)

		<b>Low ALA</b>		<b>High ALA</b>	
		<b>Low n-6</b>	<b>High n-6</b>	<b>Low n-6</b>	<b>High n-6</b>
<b>Sudden Death</b>	<i>Age-adjusted</i>	1.0	1.02 (0.68, 1.53)	1.07 (0.73, 1.58)	1.17 (0.84, 1.64)
	<i>Multivariate</i>	1.0	0.88 (0.56, 1.36)	0.95 (0.64, 1.43)	0.93 (0.64, 1.35)
<b>Non-Fatal MI</b>	<i>Age-adjusted</i>	1.0	1.04 (0.89, 1.20)	0.90 (0.77, 1.05)	1.03 (0.90, 1.16)
	<i>Multivariate</i>	1.0	0.98 (0.84, 1.15)	0.85 (0.72, 0.99)*	0.89 (0.77, 1.02)
<b>Total CHD</b>	<i>Age-adjusted</i>	1.0	0.99 (0.88, 1.12)*	0.94 (0.83, 1.06)	1.03 (0.93, 1.14)
	<i>Multivariate</i>	1.0	0.93 (0.82, 1.07)	0.88 (0.78, 0.99)*	0.89 (0.79, 0.99)*

### Other Findings

High intake of EPA and DHA intake (more than 100mg per day) compared to low intake (less than 100mg per day) was associated with a 35% lower risk of sudden death ( $HR=0.65$ ; 95% CI=0.47 to 0.88). High intake of EPA and DHA is associated with reduced sudden death regardless of ALA level.

Among men with low intakes of EPA and DHA (less than 100mg per day) each one gram per day of ALA intake was associated with a 47% ( $HR=0.53$ ; 95% CI=0.34 to 0.83) lower relative risk of total CHD and 58% lower relative risk of non-fatal MI ( $HR=58\%$ , 95% CI=0.23 to 0.75). In men with high EPA and DHA intake, there was no association between ALA and CHD.

Data are presented as relative risk plus 95% CI, with low n-6 PUFA, low EPA and DHA as

referent. Items designated with an asterisk (\*) are statistically significant.

### Author Conclusion:

n-3 DHA and EPA intake may lower risk of sudden death regardless of n-6 intake. This effect occurred at a modest intake of EPA and DHA (250mg or more per day) equivalent to one to two fish meals per week.

### Reviewer Comments:

#### Research Design and Implementation Criteria Checklist: Primary Research

##### Relevance Questions

- |    |   |     |
|----|---|-----|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?   | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?  | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies)  | Yes |

##### Validity Questions

- |      |   |     |
|------|---|-----|
| 1.   | <b>Was the research question clearly stated?</b>  | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?   | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated?  | Yes |
| 1.3. | Were the target population and setting specified?   | Yes |
| 2.   | <b>Was the selection of study subjects/patients free from bias?</b>   | ??? |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |
| 2.2. | Were criteria applied equally to all study groups?  | N/A |
| 2.3. | Were health, demographics, and other characteristics of subjects described?   | Yes |

2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
<b>3.</b>	<b>Were study groups comparable?</b>	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	Yes
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
<b>4.</b>	<b>Was method of handling withdrawals described?</b>	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
<b>5.</b>	<b>Was blinding used to prevent introduction of bias?</b>	No
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	No

5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
<b>6.</b>	<b>Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?</b>	N/A
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	???
6.6.	Were extra or unplanned treatments described?	Yes
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
<b>7.</b>	<b>Were outcomes clearly defined and the measurements valid and reliable?</b>	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	N/A
<b>8.</b>	<b>Was the statistical analysis appropriate for the study design and type of outcome indicators?</b>	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes

8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
<b>9.</b>	<b>Are conclusions supported by results with biases and limitations taken into consideration?</b>	<b>Yes</b>
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
<b>10.</b>	<b>Is bias due to study's funding or sponsorship unlikely?</b>	<b>No</b>
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes

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