

Citation:

Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. N-3 polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am J Clin Nutr.* 2003 Feb; 77 (2): 319-325.

PubMed ID: [12540389](#)

Study Design:

Prospective nested case-control

Class:

C - [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 associations of plasma phospholipid concentrations of N-3 PUFAs (DHA and EPA from fatty fish and a-linolenic acid from vegetable oils) as biomarkers of intake, with the risk of incident fatal IHD and incident non-fatal MI, in older adults.

Inclusion Criteria:

- Cardiovascular Health Study participants (65 years of age or older, from NC, CA, MD, PA)
- Free of IHD and stroke at baseline.

Exclusion Criteria:

Cases and controls using fish oil supplements at baseline.

Description of Study Protocol:**Study Participants**

- *Cases*: Experienced an incident fatal ischemic heart disease event (fatal MI or other ischemic heart disease event) during follow-up between 1989 and 1996
- *Controls*
 - Randomly chosen
 - Were free of ischemic heart disease during follow-up and were matched for same sex, clinical site and entry cohort, similar age and follow-up at least as long as that of the case.

Baseline and at Year Three of Follow-Up

- Clinical exam (sitting BP, anthropometric measurements)
- Blood samples (plasma phospholipid concentrations of N-3 PUFAs and linoleic acid)
- Questionnaires on medical history, health status and personal habits.

Data Collection Summary:

- Blood samples used were those collected closest before the IHD event or at three years
- Plasma total lipids, phospholipid PUFAs (DHA, EPA, a-linolenic acid, and linoleic acid)
- Lab personnel were blinded to case-control status.

Description of Actual Data Sample:

	Cases, Fatal IHD N=54	Controls N=54	Cases, Non-Fatal IHD N=125	Controls N=125
Age, Years	79±7.5	78.2±6.8	75.4±5.5	75.2±5.5
Male, Percentage	57.4	57.4	64.0	64.0
White, Percentage	81.5	87.0	86.4	86.4
High School Graduate, Percentage	55.6	72.2	68.8	71.8
Congestive Heart Failure, Percentage	9.3	3.7	3.2	1.6
Treated DM, Percentage	24.1	14.8	15.2	10.5
Treated Hypertension, Percentage	42.6	31.5	40.0	29.0
Weight, kg	71.4±13.9	74.5±13.0	73.5±13.8	74.9±14.1
Systolic Blood Pressure, mmHg	140.4±21.2	133.7±21.6	143.5±20.7	137.3±21.8
Diastolic Blood Pressure, mmHg	71.0±12.2	69.6±9.8	73.0±11.4	73.3±10.8
Family History of MI, Percentage	35.4	31.1	35.9	23.7
Current Smoker, Percentage	18.5	7.4	9.6	8.8
Alcohol Use, Percentage	31.5	46.3	49.6	52.0
Daily Aspirin Use, Percentage	16.7	22.2	18.4	15.2
Total Cholesterol, mmol per L	5.1±1.0	5.3±1.0	5.3±1.1	5.3±1.0
HDL Cholesterol, mmol per L	1.3±0.3	1.3±0.3	1.3±0.4	1.4±0.4
Triacylglycerol, mmol per L	1.7±0.9	1.6±0.8	1.7±0.9	1.6±0.9
Fasting Glucose, mmol per L	7.5±3.5	5.9±1.2	6.3±2.0	6.5±3.6
Fasting Insulin, mmol per L	27.0±57.4	16.0±12.1	17.9±31.6	13.8±12.1
Fibrinogen, micromol per L	9.8±1.9	9.3±1.6	9.8±1.7	9.6±2.7

Means ±SD.

Of the 54 fatal IHD cases, 36 (67%) due to arrhythmia, nine to CHF, two to other mechanisms, seven to unknown mechanisms.

Summary of Results:

Traditional IHD risk factors were generally more prevalent in cases than in controls. Cases of fatal IHD had on average higher fasting plasma glucose concentrations than did their matched controls (P=0.002)

and cases of non-fatal MI were more likely than matched controls to have a higher SBP ($P=0.02$) and to have a family history of heart disease ($P=0.047$). Cases of fatal IHD were on average older than cases of nonfatal MI ($P=0.0003$).

Overall, subjects who experienced an incident fatal IHD event had significantly lower baseline plasma phospholipid concentrations of combined DHA and EPA than matched controls ($P=0.02$) and higher concentrations of linoleic acid ($P=0.03$). In contrast, mean baseline PUFA concentrations did not differ significantly among participants who subsequently experienced a nonfatal MI and their matched controls.

After adjustment for risk factors, a higher concentration of combined DHA and EPA was associated with a lower risk of fatal IHD. For a one-SD increase in plasma phospholipid DHA and EPA, there was an associated 70% lower risk of fatal IHD (odds ratio, 0.30; 95% CI: 0.12, 0.76; $P=0.01$). Similarly, for a one-SD increase in α -linolenic acid, there was an associated 50% lower risk of fatal IHD (odds ratio, 0.48; 95% CI: 0.24, 0.96; $P=0.04$). In contrast, linoleic acid was associated with a higher risk of incident-fatal IHD. None of the PUFAs were associated with the risk of non-fatal MI.

Further adjustments for smoking, alcohol use, triacylglycerol concentrations, HDL-cholesterol concentrations, treated hypertension, treated DM, congestive heart failure, claudication, heart rate, family history of MI, fibrinogen concentrations and kcalories of physical activity did not change results.

When the analyses of fatal IHD were limited to only the cases for which the mechanism was thought to be life-threatening arrhythmia (36 cases), the estimated OR of fatal IHD associated with each one-SD increase in plasma phospholipid concentrations of DHA+EPA, α -linolenic acid and linoleic acid were 0.23 (95% CI: 0.06, 0.83), 0.43 (95% CI: 0.17, 1.12) and 2.66 (95% CI: 1.04, 6.79), respectively, after adjustment for age, weight and fasting plasma glucose concentrations.

Plasma phospholipid concentrations of linoleic acid were inversely related to concentrations of combined DHA and EPA ($R=-0.33$, $P<0.001$) and positively related to concentrations of α -linolenic acid ($R=0.30$, $P<0.0001$). Similar results were obtained when the associations of combined DHA and EPA and α -linolenic acid were investigated simultaneously or separately. When the association of all three types of PUFAs were investigated simultaneously, the association of linoleic acid with fatal IHD was noticeably diminished.

Author Conclusion:

- In this nested case-control study conducted among older adults, we found that higher plasma phospholipid concentrations of the long-chain N-3 PUFAs, DHA and EPA were associated with a lower risk of incident fatal IHD, whereas the intermediate-chain N-3 PUFA α -linolenic acid was associated with a tendency to lower risk
- In contrast, higher concentrations of linoleic acid, an N-6 PUFA, were not associated with a lower risk of fatal IHD
- None of these PUFAs were associated with the risk of non-fatal MI
- In conclusion, our results suggest that in older adults, higher dietary intake late in life of the long-chain N-3 PUFAs, DHA and EPA found in fatty fish, is associated with a lower risk of fatal IHD
- Higher dietary intake of the intermediate-chain N-3 PUFA α -linolenic acid, found in canola oil and soybean oil, also appears to be associated with a lower risk of fatal IHD
- Association of the N-3 PUFAs with lower risk of fatal IHD, but not non-fatal MI, is consistent with possible antiarrhythmic properties of N-3 PUFAs.

Reviewer Comments:

- *Author notes that the strengths of the study include prospective study design, reliable ascertainment of cardiovascular events and the availability of information on numerous clinical characteristics*

collected from study participants

- Study limitations include the relatively small number of incident-fatal IHD events and the indirect assessment of dietary PUFAs.

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. | Was the research question clearly stated? | 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. | Was the selection of study subjects/patients free from bias? | Yes |
| 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? | Yes |
| 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 |
| 3. | Were study groups comparable? | Yes |
| 3.1. | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) | Yes |
| 3.2. | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? | No |
| 3.3. | Were concurrent controls used? (Concurrent preferred over historical controls.) | Yes |

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?	N/A
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
4.	Was method of handling withdrawals described?	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
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%.)	N/A
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
5.	Was blinding used to prevent introduction of bias?	Yes
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.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	Yes
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Yes
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?	N/A
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?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
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?	Yes
7.	Were outcomes clearly defined and the measurements valid and reliable?	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?	Yes
8.	Was the statistical analysis appropriate for the study design and type of outcome indicators?	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
9.	Are conclusions supported by results with biases and limitations taken into consideration?	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	Is bias due to study's funding or sponsorship unlikely?	Yes

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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