Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies

Harris, W. S., Tintle, N. L., Imamura, F., Qian, F., Korat, A., Marklund, M., Djoussé, L., Bassett, J. K., Carmichael, P. H., Chen, Y. Y., Hirakawa, Y., Küpers, L. K., Laguzzi, F., Lankinen, M., Murphy, R. A., Samieri, C., Senn, M. K., Shi, P., Virtanen, J. K., Brouwer, I. A., … Fatty Acids and Outcomes Research Consortium (FORCE) (2021). Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies. Nature communications, 12(1), 2329. https://doi.org/10.1038/s41467-021-22370-2

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BACKGROUND

- Studies have reported inverse relations between n-3 PUFA biomarkers and total mortality.

- No meta-analysis has yet examined the relationship between LC n-3 PUFAs blood levels and risk for all-cause mortality.

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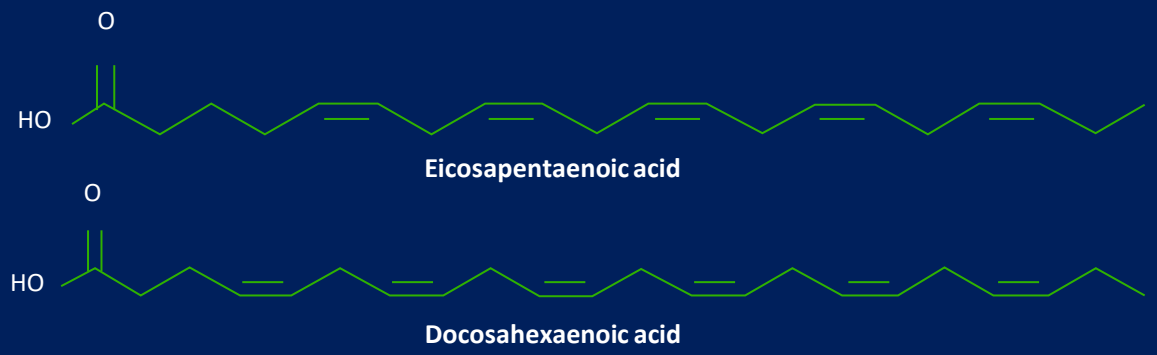

AIM

The aim of this meta-analysis was to explore the associations of circulating levels of n-3 PUFAs (both plant- and seafood-derived) and all-cause mortality, as well as mortality from CVD, cancer and all other causes.

METHODS

- 17 prospective cohort studies across 10 countries, from the Fatty Acid and Outcome Research Consortium (FORCE) with available data on circulating PUFA levels at baseline and mortality follow-up were included.

- **Study participants in the included cohorts:**
  - were >18 years old
  - had no major medical diagnoses before enrolment like myocardial infarction, stroke, or severe active cancer.
  - were not taking supplemental fish oil
  - did not die within a year of baseline

Participating studies measured PUFAs in at least one blood compartment, including plasma phospholipids, cholesterol esters, erythrocytes, and whole plasma. All PUFA levels were reported as a percent of total fatty acids.

Primary endpoint of the study was total mortality (death from any cause).

Secondary endpoints included deaths from CVD, cancer, and other causes like renal, liver or lung diseases.

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METHODS

To allow comparison and pooling of results from different biomarker compartments, n-3 PUFA levels were standardized to the study-specific inter-quintiles range, which allowed comparisons between the top and bottom 10% values of circulating n-3 PUFA.

Prespecified covariates included in data analysis (a.o.):

- Age
- Sex
- Race
- Body-mass index
- Education
- Occupation
- Marital status
- Smoking
- Physical activity
- Alcohol intake
- Prevalent diabetes mellitus
- Prevalent hypertension
- Prevalent dyslipidaemia
- Circulating n-6 PUFA levels

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RESULTS I

- At baseline, the average age was 65 years (range of mean ages across cohorts was 50–81 years), 55% were women (range of 0–100% across cohorts).
- Over a median of 16 years of follow-up (5-32 years observation), 15,720 deaths (37%) occurred among 42,466 individuals.
- Overall, approximately 30% of the deaths were attributed to CVD, 30% to cancer, and the remaining 39% to all other causes.

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RESULTS II

All Cause Mortality

– Significant differences were observed for EPA, DPA, DHA, and EPA + DHA (all < 0.01) when comparing the top to the bottom quintile. Each was associated with 15–18% lower risk of death.

– The relationship of EPA with mortality was most pronounced at lower levels and then appeared to plateau at higher levels.

– ALA was not significantly associated with total mortality.

Disease Related Mortality

– Comparing the 90th to the 10th percentile, each of the LC n-3 PUFAs was significantly associated with a lower risk for death from CVD, cancer, and all other causes combined. One exception: DHA and cancer mortality.

– ALA was not significantly associated with any cause-specific mortality.

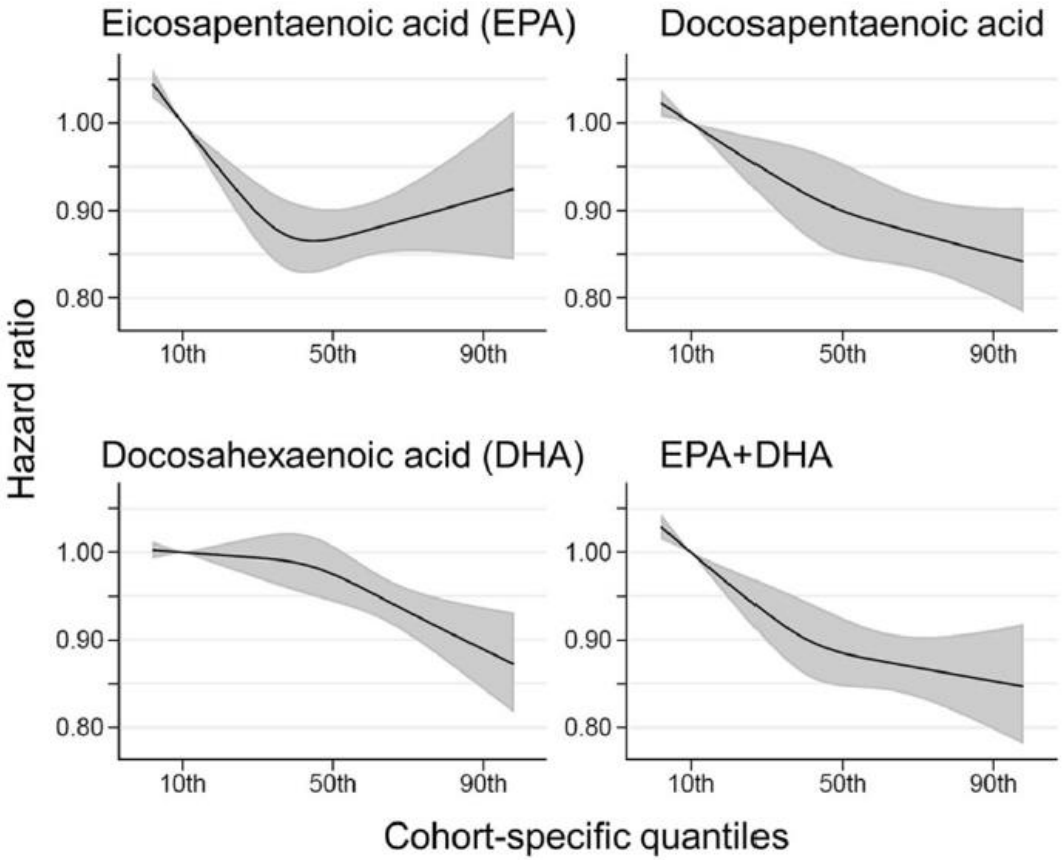

Fig. Associations of circulating long-chain n-3 PUFA levels with all cause mortality: nonlinear dose-response meta-analysis in the Fatty Acids and Outcomes Research Consortium. Hazard ratios and cohort specific quantiles are presented in the vertical and horizontal axis, respectively.

CONCLUSION

"In summary, in a global pooled analysis of prospective studies, LC n-3 PUFA levels were inversely associated with risk for death from all causes and from CVD, cancer, and other causes".

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ARTICLE

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Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies

William S. Harris[1,2✉], Nathan L. Tintle[2,3], Fumiaki Imamura[4], Frank Qian[5,6], Andres V. Ardisson Korat[6], Matti Marklund[7,8], Luc Djoussé[6], Julie K. Bassett[9], Pierre-Hugues Carmichael[10], Yun-Yu Chen[11], Yoichiro Hirakawa[12], Leanne K. Küpers[13], Federica Laguzzi[14], Maria Lankinen[15], Rachel A. Murphy[16], Cécilia Samieri[17], Mackenzie K. Senn[18], Peilin Shi[19], Jyrki K. Virtanen[15], Ingeborg A. Brouwer[20], Kuo-Liong Chien[21,22], Gudny Eiriksdottir[23], Nita G. Forouhi[4], Johanna M. Geleijnse[13], Graham G. Giles[24], Vilmundur Gudnason[23,25], Catherine Helmer[17], Allison Hodge[24], Rebecca Jackson[26], Kay-Tee Khaw[4], Markku Laakso[27], Heidi Lai[19,28], Danielle Laurin[10,29], Karin Leander[14], Joan Lindsay[30], Renata Micha[19], Jaako Mursu[15], Toshiharu Ninomiya[31], Wendy Post[9], Bruce M. Psaty[32], Ulf Risérus[33], Jennifer G. Robinson[34,35], Aladdin H. Shadyab[36], Linda Snetselaar[35], Aleix Sala-Vila[2,37], Yangbo Sun[35,38], Lyn M. Steffen[39], Michael Y. Tsai[40], Nicholas J. Wareham[4], Alexis C. Wood[18], Jason H. Y. Wu[7], Frank Hu[5,6], Qi Sun[5,6], David S. Siscovick[41], Rozenn N. Lemaitre[32], Dariush Mozaffarian[19] & The Fatty Acids and Outcomes Research Consortium (FORCE)*

The health effects of omega-3 fatty acids have been controversial. Here we report the results of a de novo pooled analysis conducted with data from 17 prospective cohort studies examining the associations between blood omega-3 fatty acid levels and risk for all-cause mortality. Over a median of 16 years of follow-up, 15,720 deaths occurred among 42,466 individuals. We found that, after multivariable adjustment for relevant risk factors, risk for death from all causes was significantly lower (by 15–18%, at least $p < 0.003$) in the highest vs the lowest quintile for circulating long chain (20–22 carbon) omega-3 fatty acids (eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids). Similar relationships were seen for death from cardiovascular disease, cancer and other causes. No associations were seen with the 18-carbon omega-3, alpha-linolenic acid. These findings suggest that higher circulating levels of marine n-3 PUFA are associated with a lower risk of premature death.

A full list of author affiliations appears at the end of the paper.

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