Bioactive omega-3 fatty acids are associated with reduced risk and severity of SARS-CoV-2 infection

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In this issue of the *American Journal of Clinical Nutrition*, Harris et al. (1) report that a higher status of the bioactive omega-3 fatty acid docosahexaenoic acid (DHA) is associated with a lower risk of testing positive for SARS-CoV-2 and of being hospitalized with the disease it causes, COVID-19. DHA and its precursor eicosapentaenoic acid (EPA) are obtained from the diet, with the richest source being seafood, especially fatty fish, and are also found in "fish oil" supplements. Circulating levels of EPA and DHA are higher in those who consume fatty fish regularly and in those who use "fish oil" supplements. Harris et al. (1) used data from the UK BioBank, a prospective, population-based cohort of approximately 500,000 individuals recruited between 2007 and 2010 at assessment centers across England, Wales and Scotland (2, 3). Baseline data derived from questionnaires, biological samples and physical measurements were collected on all participating individuals, with longitudinal monitoring occurring via a mix of in-person and electronic medical record data. From the entire UK Biobank population, a random subset of non-fasting baseline plasma samples from 118,466 individuals had been analysed using high-throughput NMR spectroscopy. Harris et al. (1) used

data on 110,584 of these individuals to assess the association between DHA status and hospitalisation with or mortality from COVID-19. Furthermore, they used data on 26,594 individuals for whom information was available on the outcome of a test for infection with SARS-CoV-2 to assess the association with DHA status. These outcomes were assessed between 1 January 2020 and 23 March 2021. Included participants had mean age 68 yr, were mainly white and were roughly evenly distributed between the sexes. A positive test for SARS-CoV-2 infection was reported for 15% of those tested, while less than 1% of the participants were hospitalized with COVD-19; of these, 20% died. Mean plasma DHA was 2% of total fatty acids; Harris et al. (1) used an existing algorithm to calculate a mean omega-3 index (EPA plus DHA in red blood cells) of 5.6%.

Harris et al. (1) report an inverse association for a positive test for SARS-CoV-2 infection and for hospitalisation with COVID-19 across quintiles of plasma DHA. In unadjusted analysis, the hazard ratio for testing positive for SARS-CoV-2 in the highest compared with the lowest quintile of plasma DHA was 0.60 (95% CI: 0.55, 0.67; $p < 0.001$) while for hospitalisation with COVID-19 it was 0.48 (95% CI: 0.38, 0.60; $p < 0.001$). Data were adjusted with three models that included age at the start of the pandemic, sex, and race; age at the start of the pandemic, sex, race and waist circumference; and age at the start of the pandemic, sex, race, waist circumference, Townsend Deprivation Index, time since enrolment, smoking status, education, self-reported health, blood pressure, slow walking pace, and intake of fresh fruit, dried fruit, fresh vegetables, cooked vegetables and grain fiber. The protective association of DHA towards both outcomes was maintained with these adjustments. In the most fully adjusted analysis, the hazard ratio for testing positive for SARS-CoV-2 in the highest compared with the lowest quintile of plasma DHA was 0.79 (95% CI: 0.71, 0.89; $p < 0.001$) while for hospitalisation with COVID-19 it was 0.74 (95% CI: 0.55, 0.94; $p < 0.05$). Both outcomes showed a significant inverse linear trend across quintiles for unadjusted and all adjusted analyses ($p < 0.001$ in all cases). Findings for mortality from COVID-19 were slightly different: the hazard ratio in the second highest compared with the lowest quintile of plasma DHA was 0.42 (95% CI: 0.27, 0.66; $p < 0.001$) in the unadjusted analysis and 0.61 (95% CI: 0.39, 0.98; $p < 0.05$) in the fully adjusted analysis. However, the hazard ratio was not different between the highest and lowest quintiles of plasma DHA; this suggests a U-shaped association between DHA status and mortality from COVID-19.

Harris et al (1) are not the first to report inverse associations been long-chain omega-3 fatty acids and SARS-CoV-2-related outcomes (4-10). Using the same UK BioBank dataset as Harris et al. (1), Julkenen et al. (4) reported that higher plasma DHA was associated with lower

risk of being hospitalized with COVID-19 in an age- and sex-adjusted model; unlike Harris et al. (1) they did not adjust for any other covariates or report on the effect of DHA on test positivity or mortality. Using UK BioBank data, Sun et al. (5) reported that plasma DHA was inversely associated with testing positive for SARS-CoV-2 (odds ratio 0.91, 95% CI: 0.87, 0.94) and hospitalisation with COVID-19 (odds ratio 0.78, 95% CI: 0.72, 0.85) after adjustment for age, sex, ethnicity, body mass index, Townsend deprivation index, and assessment center. Fish oil use was recorded in the UK BioBank and from 110,440 participants 26.6% reported habitual use of fish oil supplements. Ma et al. (6) reported that habitual fish oil use was associated with lower risk of hospital admission with COVID-19 (hazard ratio 0.79, 95% CI: 0.69, 0.83) and mortality from COVID-19 (hazard ratio 0.69, 95% CI: 0.58, 0.83) after adjustment for age and sex and this remained significant after further adjustment for age, sex and multiple other covariates. Beyond UK BioBank, a study based upon self-reporting through a mobile phone application identified that among 372,720 UK participants who had a test for infection with SARS-CoV-2 (6.3% tested positive), users of fish oil supplements had a 12% lower risk of testing positive for SARS-COV-2 than non-users, after adjusting for age, sex, body mass index, sign-up health status and multiple testing (7). Similar lower risk for testing positive in fish oil supplement users was observed among smaller numbers of participants from the US (n = 45,757) and Sweden (n = 27,377) (7). Omega-3 index was measured in 100 patients hospitalized with COVID-19 in the US (59% men, mean age 72.5 yr), 14 of whom went on to die (8). After adjusting for age and sex, the odds ratio for death in patients with an omega-3 index in quartile 4 versus those with an omega-3 index in quartiles 1 to 3 was 0.25 (95% CI: 0.03, 1.11; p = 0.07). In a case-control design study from Chile hospitalized patients with severe SARS-CoV-2 infection (n = 73) had a lower omega-3 index than a group of ambulatory patients with mild SARS-CoV-2 infection (controls, n = 71) (9). Amongst the patients with severe COVID-19 there was an inverse association between omega-3 index and need for mechanical ventilation (odds ratio 0.46, 95% CI: 0.21, 0.99) and death (odds ratio 0.28, 95% CI: 0.08, 0.985), even after adjusting for sex, age, body mass index, comorbidities and tobacco use (10).

A number of association studies, including those using the large UK BioBank dataset indicate that higher DHA status is associated with lower risk of testing positive for SARS-CoV-2, being hospitalized with COVID-19 and severe outcome from COVID-19. Even with the multiple adjustments for covariates used in most of those studies, they remain observational and cause and effect cannot be inferred. This requires controlled trials. So far there are few such trials. Doaei et al. (11) randomized critically ill patients with COVID-19 to a high protein enteral formula providing 400 mg EPA and 200 mg DHA daily for 14 days (n = 42) or to a

control group that received the formula without added omega-3 fatty acids (n = 86). The omega-3 group had better indicators of some, but not all, physiological functions at day 14 and had better survival at one month (21% vs 3%, p = 0.003).

Understanding possible mechanisms of action of the protective effect of omega-3 fatty acids, and DHA in particular, would add plausibility to the associations described. In this respect the lower risks of testing positive for SARS-CoV-2 and of COVID-19 being more severe, requiring hospitalisation and leading to mortality need to be considered separately. Testing positive for SARS-CoV-2 obviously requires exposure to the virus. This is why strategies such as hand washing, wearing face masks, social distancing and isolation are effective in reducing infection risk. It is possible that those with higher DHA status, which would most likely result from eating fatty fish or using omega-3 supplements, show greater compliance with health behaviors that limit exposure to SARS-CoV-2 and therefore are less likely test positive. However, it is also possible that DHA has effects that restrict viral entry to host cells, limit viral replication or promote virus elimination, so that post-SARS-CoV-2 exposure, evidence of infection is absent. One example of such an effect is that DHA, and also EPA, may hold the spike glycoprotein of SARS-CoV-2 in a closed configuration that is unable to bind to the ACE2 receptor on host cells (12) so preventing viral entry. EPA is also able to inhibit the activity of key proteases that cleave spike proteins to enable viral entry (13); DHA seems not to have been tested in this regard. Coronaviruses are known to use the sterol regulatory element binding protein dependent pathway for replication; omega-3 fatty acids are inhibitors of gene transcription and protein maturation of sterol regulatory element binding proteins (14) which may act to suppress viral replication. Hence there are several possible sites of action for long-chain omega-3 fatty acids to inhibit SARS-CoV-2 entry into host cells and replication, effects that would result in lower risk of testing positive. Of course, such effects would also be important in an infected individual and would act to restrict an increase in viral load so contributing to a better prognosis and less likelihood of progression to more severe disease requiring hospitalisation and resulting in death. However, other actions of DHA are likely to be important in this regard also. A heightened inflammatory response is linked to more severe COVID-19 and poor outcome (15-17). Omega-3 fatty acids including DHA have multiple anti-inflammatory actions (18) that might limit harmful exaggerated inflammation so decreasing the risk of progression to more severe disease. DHA is also a precursor for specialized pro-resolution mediators (SPMs), several of which are beneficial in rodent models of respiratory disease and infection (19). Higher plasma DHA would link with higher levels

of SPMs (20), in turn helping to control exaggerated inflammation and decreasing risk of more severe COVID-19.

The research of Harris et al (1) extends the earlier studies based on the UK BioBank dataset (4-6) and offers are more complex analysis of these data. The research of Harris et al. (1) has strengths and weaknesses. Strengths include the large sample size and the statistical adjustments made to the data. One limitation of the findings is that vaccination was introduced in the UK during the follow-up period and participants' vaccination status is not known.

In summary, using the large UK BioBank dataset Harris et al. (1) report that higher DHA status is associated with lower risk of becoming infected with SARS-CoV-2 and of being hospitalized with COVID-19, There is also an indication that higher DHA status is associated with reduced risk of mortality for COVID-19, although this effect was attenuated at the very highest status level. These findings suggest that consuming more long-chain omega-3 fatty acids (EPA and DHA) should be encouraged as a strategy to reduce the impact of the on-going SARS-CoV-2 pandemic and of future respiratory virus infection outbreaks. Increased intake of EPA and DHA can be achieved through consumption of fatty fish or use of supplements containing EPA and DHA.

References

1. Harris WS, Tintle NL, Perinkulam Sathyanarayanan S, Westa J. Association between blood n-3 fatty acid levels and risk for COVID-19 in the UK biobank. American Journal of Clinical Nutrition 2023;in press.
2. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Medicine 2015;12:e1001779.
3. Collins R. What makes UK Biobank special? Lancet 2012;379:1173-1174.
4. Julkunen H, Cichońska A, Slagboom PE, Würtz P, Nightingale Health UKBI. Metabolic biomarker profiling for identification of susceptibility to severe pneumonia and COVID-19 in the general population. eLife 2021;10:e63033.
5. Sun Y, Chatterjee R, Ronanki A, Ye K. Circulating polyunsaturated fatty acids and COVID-19: A prospective cohort study and mendelian randomization analysis. Frontiers in Medicine 2022;9:923746.
6. Ma Y, Zhang L, Zeng R, Luo D, Jiang R, Wu H, et al. Associations of habitual fish oil use with risk of SARS-CoV-2 infection and COVID-19-related outcomes in UK: national population based cohort study. medRxiv 2022:2022.09.14.22279933.

7. Louca P, Murray B, Klaser K, Graham MS, Mazidi M, Leeming ER, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. BMJ Nutrition Prevention and Health 2021;4:149-157.
8. Asher A, Tintle NL, Myers M, Lockshon L, Bacareza H, Harris WS. Blood omega-3 fatty acids and death from COVID-19: A pilot study. Prostaglandins, leukotrienes, and Essential Fatty Acids 2021;166:102250.
9. Ramírez-Santana M, Zapata Barra R, Ñunque González M, Müller JM, Vásquez JE, Ravera F, et al. Inverse association between omega-3 index and severity of COVID-19: a case-control study. International Journal of Environmental Research and Public Health 2022;19:6445.
10. Zapata BR, Müller JM, Vásquez JE, Ravera F, Lago G, Cañón E, et al. Omega-3 index and clinical outcomes of severe COVID-19: preliminary results of a cross-sectional study. International Journal of Environmental Research and Public Health 2021;18:7722.
11. Doaei S, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F, Bagheri SE, et al. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. Journal of Translational Medicine 2021;19:128.
12. Vivar-Sierra A, Araiza-Macías MJ, Hernández-Contreras JP, Vergara-Castañeda A, Ramírez-Vélez G, Pinto-Almazán R, et al. In silico study of polyunsaturated fatty acids as potential SARS-CoV-2 spike protein closed conformation stabilizers: epidemiological and computational approaches. Molecules 2021;26,711.
13. Goc A, Niedzwiecki A, Rath M. Polyunsaturated ω-3 fatty acids inhibit ACE2-controlled SARSCoV-2 binding and cellular entry. Scientific Reports 2021;11:5207.
14. Jump DB, Botolin D, Wang Y, Xu J, Demeure O, Christian B. Docosahexaenoic acid (DHA) and hepatic gene transcription. Chemistry and Physics of Lipids 2008;153:3-13.
15. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.
16. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. Journal of Clinical Investigations 2020;130:2620-2629.

17. Ruan Q, Yang K, Wang W, Jiang L Song4 J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine 2020, 46.846–848.
18. Calder, P.C., n-3 PUFA and inflammation: from membrane to nucleus and from bench to bedside. Proceedings of the Nutrition Society 2020;79:404-416.
19. Cagnina RE, Duvall MG, Nijmeh J, Levy BD. Specialized pro-resolving mediators in respiratory diseases. Current Opinion in Clinical Nutrition and Metabolic Care 2022;25:67-74.
20. Calder, P.C., Eicosapentaenoic and docosahexaenoic acid derived specialised pro-resolving mediators: Concentrations in humans and the effects of age, sex, disease and increased omega-3 fatty acid intake. Biochimie 2020;178:105-123.