The protective effect of omega-3 fatty acids in attenuating lung function decline

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Chronic obstructive pulmonary disease (COPD), characterized by persistent respiratory symptoms and airflow limitation, is a preventable and treatable disease that remains one of the top five leading causes of death in the United States. About 6.4% of Americans have been diagnosed with COPD, but this is only an underestimate because over half of the adults with low pulmonary function did not receive a diagnosis (1). Omega-3 fatty acids have been associated with better lung function and reduced risk of COPD. However, results from cross-sectional studies of circulating biomarkers or longitudinal studies of dietary intakes have been inconclusive (2, 3). Here, Patchen *et al.* investigated the role of omega-3 fatty acids in lung function by triangulating evidence from two less confounded study designs (4). They focused on the circulating levels of omega-3 fatty acids, bypassing the potential reporting bias and estimation inaccuracy in dietary intakes (5). The outcomes of interest were defined with spirometry, including forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and airway obstruction as $FEV_1/FVC < 70\%$. First, they performed a longitudinal study in generally healthy adults of diverse race and ethnicity by pooling four cohorts from the NHLBI Pooled Cohorts Study. Second, they performed two-sample Mendelian randomization (MR) analysis by leveraging existing genome-wide association studies (GWAS) of the exposures and outcomes. The longitudinal design is well-known to mitigate the concern of reverse causation. The genetics-based MR approach, by leveraging the random allocation of genetic variants at conception and the natural effect direction from genes to phenotypes, has the potential for causal inference if all the underlying assumptions are met (6).

In the longitudinal study of 15,063 participants, Patchen *et al.* found that every standard deviation (SD) increment in alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) was significantly associated with an attenuation of 0.77, 0.62, and 1.77 mL/year for

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FEV_1 and 1.30, 0.84, and 2.43 mL/year for FVC. To put these numbers into context, current and former smokers have about 8 and 2 mL/year more decline in FEV_1 than non-smokers. In other words, one SD increment in DHA, which is achievable with a high-fish diet or omega-3 supplements, can counteract about 25% of the additional FEV_1 annual decline in current smokers and almost all the additional decline in former smokers. Moreover, with 1,455 incident cases of airway obstruction during a median follow-up period of 5 years, they found that DHA is associated with a lower risk of airway obstruction (hazard ratio per SD = 0.91, 95% CI = 0.87–0.97). This effect remained unchanged when all omega-3 fatty acids were included in the same model, suggesting that DHA mediates the effects of other omega-3 fatty acids. Additionally, interaction analysis showed that the effects of DHA largely persisted across sex, smoking history, and race and ethnicity. The association patterns of other omega-3 fatty acids, including ALA, EPA, and docosapentaenoic acid (DPA), were more complicated and varied across outcomes and subgroups. In terms of the MR study, there was a general trend of positive associations between the downstream omega-3 fatty acids (i.e., EPA, DPA, and DHA) and the two continuous outcomes, FEV_1 and FVC. Although statistical significance was limited, the overall MR results supported observations from the longitudinal study that DHA was associated with attenuated lung function decline.

Patchen *et al.* is the first study to longitudinally evaluate the association of circulating omega-3 fatty acids with lung function decline in a generally healthy adult population. Some of its observations were further supported by genetics-based MR analysis. Its usage of cohorts with diverse race and ethnicity is a strength, and its interaction analysis revealed effect modifications by biological and lifestyle factors. Notably, the associations of ALA, EPA, and DPA with

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attenuated lung function decline were mainly observed in men, white participants, and smokers, with little to no evidence for associations in women, non-white participants, and non-smokers. While it is known that omega-3 fatty acid metabolism varies across sex, race and ethnicity, and smoking, future studies are warranted to elucidate the mechanism of context-dependent effects.

Another noteworthy observation is the opposite effect directions of upstream and downstream omega-3 fatty acids, particularly ALA and DHA. These two fatty acids had a very weak positive correlation ($r = 0.03$) across all samples of the longitudinal cohorts and varied correlation patterns in subgroups. While both were positively associated with attenuated FEV_1 and FVC decline in the longitudinal study, ALA was associated with an increased risk of airway obstruction, and DHA was associated with a decreased risk. In the MR study, ALA was negatively, while DHA was positively associated with FEV_1 and FVC. These opposite association patterns may be explained by the precursor-product relationship of ALA and DHA and a causal role of DHA in protecting lung function. Indeed, when all fatty acids were included in the same model, the association of ALA with airway obstruction was attenuated in the longitudinal study, while the effect of DHA remained unchanged. On the other hand, the genetic instruments used in MR analysis were dominated by variants located in genes (e.g., *FADS1* and *FADS2*) that convert ALA to the downstream omega-3 fatty acids. Naturally, variants increasing conversion are associated with lower precursor but higher product levels. In contrast, genetic variants enhancing the absorption of all fatty acids will result in higher levels of both ALA and DHA. The former type of genetic instruments will yield opposite association directions for ALA and DHA, while the latter type will produce the same directions. Therefore, the biological function of genetic instruments is required in meaningfully interpreting MR results (7), but unfortunately, it was often neglected.

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Patchen *et al.* had thorough discussions of their study limitations, such as heterogeneity across cohorts, the usage of relative percentages in total plasma phospholipids rather than absolute concentrations for the circulating fatty acids, and the limited numbers of genetic instruments (i.e., 1 for ALA, 2 for EPA, 3 for DPA, and 5 for DHA). Excitingly, the growing availability of biobank-scale cohorts, such as UK Biobank and All of Us (8, 9), provides unprecedented opportunities to address these limitations. For example, all UK Biobank participants (N =~500,000) have spirometry measurements, and over 270,000 have metabolomic data that measured the absolute concentrations of omega-3 and omega-6 fatty acids (10, 11). GWAS of circulating fatty acids in this cohort has identified over 100 genomic loci, empowering future MR studies (12, 13). It is hopeful that these biobank-scale prospective cohorts and the application of advanced research approaches will elucidate the effects of omega-3 fatty acids on lung function and disease.

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