

Original Research

# Higher Plasma Omega-3 Levels are Associated With Improved Exacerbation Risk and Respiratory-Specific Quality of Life in COPD

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## Abstract

**Background:** Omega-3 polyunsaturated fatty acids (PUFAs) have been associated with systemic anti-inflammatory responses. Dietary intake of omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has also been associated with lower chronic obstructive pulmonary disease (COPD) morbidity using self-report food frequency questionnaires.

**Objective:** The objective of this study was to investigate the relationship between measured PUFA intake using plasma EPA+DHA levels and COPD morbidity.

**Methods:** Former smokers with moderate-to-severe COPD living in low-income communities were enrolled in a 6-month prospective cohort study. Participants completed standardized questionnaires, spirometry, and plasma samples at 3-month intervals. Total plasma PUFAs were analyzed using gas chromatography/mass spectrometry for DHA and EPA concentrations. Linear or logistic mixed model regression was used to evaluate EPA+DHA's and COPD morbidity's association, accounting for demographics, lung function, pack years, comorbidities, and neighborhood poverty.

**Results:** A total of 133 plasma EPA+DHA samples from 57 participants were available. Participants exhibited average plasma EPA and DHA levels of  $14.7 \pm 7.3 \mu\text{g/mL}$  and  $40.2 \pm 17.2 \mu\text{g/mL}$ , respectively, across the 3 clinic visits. Each standard deviation increase in EPA+DHA levels was associated with 2.7 points lower St George's Respiratory Questionnaire score (95% confidence interval [CI] -5.2, -0.2) and lower odds of moderate exacerbation (odds ratio 0.4; 95% CI 0.2, 0.9), but lacked significant association with the COPD Assessment Test score (95% CI -2.4, 0.8), modified Medical Research Council dyspnea scale (95% CI -0.2, 0.2), or severe exacerbations (95% CI 0.3, 1.4).

**Conclusion:** Plasma EPA+DHA levels are associated with better respiratory-specific quality of life and lower odds of moderate exacerbations in patients with moderate-to-severe COPD. Further research is warranted to investigate the efficacy of an omega-3 dietary intervention in the management of COPD morbidities.

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## Abbreviations:

**ALA**= $\alpha$ -linolenic acid; **BMI**=body mass index; **CAT**=COPD assessment test; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **DHA**=docosahexaenoic acid; **DPA**=docosapentaenoic acid; **EPA**=eicosapentaenoic acid; **FEV<sub>1</sub>**=forced expiratory volume in 1

second; **FEV<sub>1</sub>%pred**=forced expiratory volume in 1 second percentage predicted; **FVC**=forced vital capacity; **GLMM**=generalized linear mixed model; **ICC**=intraclass correlation; **IFN**=interferon; **IL**=interleukin; **MaR1**=Maresin-1; **mMRC**=modified Medical Research Council; **OR**=odds ratio; **PKC**=protein Kinase C; **PMN**=polymorphonuclear leukocytes; **PUFA**=polyunsaturated fatty acid; **SD**=standard deviation; **SGRQ**=St George's Respiratory Questionnaire; **SPMs**=specialized pro-resolving mediators; **TNF**=tumor necrosis factor

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**Introduction**

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in the United States<sup>1</sup> and is widely acknowledged to be associated with factors such as tobacco smoking and exposure to various irritant particles and gases.<sup>2,3</sup> There is growing awareness of the significant impact of dietary intake on respiratory health.<sup>4,5</sup> In particular, polyunsaturated fatty acids (PUFAs) are an essential source of biologically active lipid-derived anti-inflammatory and pro-resolving mediators such as resolvins, maresins, and protectins.<sup>6</sup> These pro-resolving mediators, which may act on chronic, unrestrained pulmonary inflammation, are primarily derived from omega-3 fatty acids, such as plant-sourced  $\alpha$ -linolenic acid (ALA) or fish-sourced eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)<sup>7,8</sup>—and to a lesser well-known degree, docosapentaenoic acid (DPA).<sup>9,10</sup> Previous studies have illuminated the therapeutic potential of omega-3 PUFAs in conditions such as cardiovascular disease and inflammatory bowel diseases.<sup>11,12</sup> Most research investigating the relationship between omega-3 PUFAs and respiratory disease, particularly COPD, has primarily focused on subjectively measured omega-3 intake based on participants' self-reported dietary intake, suggesting an association between EPA and DHA intake and COPD morbidity.<sup>13-15</sup> Limited studies have adopted a more objective approach to investigating the impact of blood omega-3 PUFA concentrations on COPD morbidity. Shahar et al found the prevalence of COPD inversely related to the DHA concentration in plasma lipids, suggesting that the fatty acid may have preventative and protective properties in current and former smokers.<sup>16</sup> Similarly, Patchen et al observed higher circulating omega-3 fatty acids, especially DHA, were associated with attenuated lung function decline and decreased odds of airway obstruction.<sup>17</sup> Our study advances the investigation of these relationships by utilizing objective blood-based biomarkers

to observe whether plasma concentrations of omega-3 fatty acids, specifically EPA and DHA, are associated with respiratory outcomes in former smokers with moderate-to-severe COPD. By focusing on objective biomarkers, this research seeks to further elucidate the impact of dietary intake of these omega-3 fatty acids on COPD morbidity, highlighting the role of nutritional factors in respiratory health and their potential in managing COPD.

**Methods****Study Population and Design**

This observational, 6-month prospective study utilized data from the first 57 participants who completed all visits from the urban cohort of the Comparing Urban and Rural Effects of Poverty on COPD (CURE COPD) study. The Johns Hopkins Medical Institutional Review Board approved the study (IRB00069904), and all participants provided written informed consent before beginning the study. Participants were from low-income communities in Baltimore, Maryland, who met the inclusion criteria of: (1) 40 years or older; (2) a postbronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) less than 0.70; (3) an FEV<sub>1</sub> percentage predicted (FEV<sub>1</sub>%pred) less than 80%; and (4) a former smoker (self-reported at least 6-months of smoking cessation and exhaled carbon monoxide  $\leq 6$ ppm<sup>18</sup> with at least a 10 pack-year history of tobacco use). Participants were followed at in-person study visits every 3 months (baseline, 3 months, and 6 months). Demographics, smoking history, and comorbidity were assessed by questionnaire.

**Plasma Omega-3 Fatty Acid Analysis**

Plasma was collected from participants at each study visit. Participants' plasma was analyzed for omega-3 concentrations (EPA, DHA, DPA, ALA) in absolute scale ( $\mu\text{g}/\text{mL}$ ) using the gas chromatography/mass spectrometry method.<sup>19</sup>

**Respiratory Health Outcomes**

At each study visit, questionnaires were administered, including the COPD assessment test (CAT) (measures the impact of COPD),<sup>20</sup> the modified Medical Research Council (mMRC) dyspnea scale (measures functional impairment due to dyspnea),<sup>21</sup> and the St George's Respiratory Questionnaire (SGRQ) (measures respiratory-specific quality of life).<sup>22</sup> For the SGRQ, we utilized the total score, which encompasses the overall impact of the disease on health status, including symptoms, activity, and impact components. History of moderate (oral steroid use, antibiotics use, or unscheduled physician visit due to COPD in the last 3 months) and severe exacerbations (emergency department/hospital visits due to COPD in the last 3 months) were assessed by monthly phone calls.

## Biomarkers

At each study visit, serum specimens were collected and analyzed in the clinical laboratory within 2 hours of collection, aliquoted, and stored at  $-80^{\circ}\text{C}$ . Serum biomarkers were measured using the multiplex assay process detailed in Fawzy et al<sup>23</sup> and included the following markers of inflammation: tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, IL-8, and interferon (IFN)- $\gamma$ .

## Statistical Analysis

To evaluate the relationship between plasma omega-3 levels and COPD morbidity, a generalized linear mixed model (GLMM) with a random intercept was employed.<sup>24</sup> This model is appropriate for per-measurement data (as opposed to per-patient data) by accounting for nonindependent observations within individuals, and the model adjusted for baseline covariates, including age, gender, race (White versus non-White), education (some college or above versus high school graduate or below), smoking pack years, body mass index (BMI), comorbidity count, FEV<sub>1</sub> %pred using race-neutral Global Lung Initiative equations,<sup>25</sup> and neighborhood poverty—as represented by the percentage of families living below the poverty line in a census tract.<sup>26</sup> Gaussian probability distribution with an identity link function was applied for continuous outcomes (CAT, mMRC, and SGRQ). For dichotomized exacerbation outcomes (severe and moderate), a binomial distribution with a logit link function was used. The analysis obtained the mean difference in continuous outcomes or the odds ratio for exacerbation outcomes per 1 standard deviation (SD) increase in plasma omega-3. As a secondary analysis, the relationship between plasma omega-3 and inflammatory biomarkers (TNF- $\alpha$ , IL-6, IL-8, IFN- $\gamma$ ) was assessed using the same method used for the continuous COPD outcomes; except biomarkers were log-transformed because of their skewed distributions and their associations with plasma omega-3 expressed in terms of percentage change in geometric mean concentrations per 1 SD increase in plasma omega-3. Plasma omega-3 was primarily represented by the sum of EPA and DHA (EPA+DHA), based on prior studies associating EPA+DHA intake via food frequency questionnaire with COPD morbidity.<sup>15</sup> To assess the linearity assumption in regression analysis and allow the flexible, functional shape of the association between omega-3 and COPD outcomes, a secondary analysis was also run using restricted cubic spline GLMM regression. The secondary analysis explored various representations of omega-3, including incorporating DPA and ALA as omega-3 (EPA+DHA+DPA+ALA). Additionally, the analysis evaluated EPA, DHA, DPA, and ALA separately, as well as expressing omega-3 as a percentage of total fatty acids. All analyses were performed using Stata, version 15.1 (Stata Corp, College Station, Texas). Statistical significance was defined as  $p < 0.05$ .

## Results

### Participant Characteristics

Our study's 57 participants had a mean ( $\pm$ SD) age of 65.3 years ( $\pm 8.7$ ) and a mean BMI of 32.6 ( $\pm 9.2$ ), consisting of 34 females (59.6%) and 28 persons identifying as White (49.1%) (Table 1). Participants had a mean of 51.1 pack years ( $\pm 35.4$ ) of smoking. Participants reflected a relatively low-income population, with about one-fifth of residents living in neighborhoods below the poverty line (18.1%) and almost half (45.6%) having less than a high school education. Participants had an average of 3 comorbidities ( $3.6 \pm 1.9$ ), moderate-to-severe COPD reflected by a mean FEV<sub>1</sub> %pred of 51.2% ( $\pm 15.9$ ), and patient-reported outcome scores reflecting a moderate COPD health impact.<sup>20,27,28</sup> Participants' mean plasma EPA+DHA levels were 54.02  $\mu\text{g}/\text{mL}$  ( $\pm 22.2$ ) with a mean plasma EPA of 14.7  $\mu\text{g}/\text{mL}$  ( $\pm 7.3$ ) and mean DHA of 40.2  $\mu\text{g}/\text{mL}$  ( $\pm 17.2$ ) (Figure 1). There was also some within-person variability in plasma EPA+DHA, with the intraclass correlation (ICC) of 0.81 and within-person standard deviation of 9.7  $\mu\text{g}/\text{mL}$ ; for EPA, the ICC and within-person SD were 0.71 and 4.0  $\mu\text{g}/\text{mL}$ , respectively while for DHA 0.81 and 7.5  $\mu\text{g}/\text{mL}$ . In comparison, the between-person SD of EPA+DHA, EPA, and DHA were 19.8, 6.2, and 15.4  $\mu\text{g}/\text{mL}$  respectively. Out of 57 participants with plasma omega-3 data, 84% (48 out of 57) had omega-3 measured across multiple visits (28 participants in all 3 visits and 20 in 2 visits), while 9 participants had omega-3 data in just one visit.

### Association of Eicosapentaenoic Acid+Docosahexaenoic Acid Levels With COPD Morbidity and Inflammatory Biomarkers

After adjusting for covariates, higher EPA+DHA plasma levels were associated with lower SGRQ and lower risk of moderate exacerbations (Table 2 and Figure 2). Specifically, a 1 SD ( $\sim 22.2 \mu\text{g}/\text{mL}$ ) increase in EPA+DHA levels was associated with a 2.7 points lower SGRQ score, reflecting better respiratory-specific quality of life (95% confidence interval [CI] -5.2, -0.2;  $p = 0.04$ ). Protective associations of EPA+DHA were also demonstrated for moderate exacerbations, with a 1 SD increase in EPA+DHA levels associated with 60% lower odds of moderate exacerbations (odds ratio [OR] 0.40; 95% CI 0.2, 0.9;  $p = 0.02$ ). Although omega-3 showed a trend towards better COPD metrics for other respiratory health outcomes (i.e., 0.8 points lower CAT [95% CI -2.4, 0.8,  $p = 0.3$ ]) and 30% lower odds of severe exacerbations (OR 0.7; 95% CI 0.3, 1.4,  $p = 0.3$ ), neither reached statistical significance. Plasma EPA+DHA showed no trends with mMRC ( $p = 0.7$ ). The results were similar in sensitivity analyses, which only included participants who had omega-3 data on multiple visits (data not shown).



**Table 1. Baseline Participant Characteristics**

	Mean±SD or n (%)	Range
Age, y	65.28±8.70	(49.0 – 81.0)
Sex, n (% Female)	34 (59.6%)	
Race, n (% White)	28 (49.1%)	
Education, n (% High School Grad or Above)	31 (54.4%)	
Pack Years	51.12±35.39	(10.0 – 175.0)
Comorbidity, Count	3.56±1.93	(0.0 – 8.0)
Body Mass Index	32.63±9.18	(16.9 – 64.0)
Post FEV <sub>1</sub> %Pred	51.24±15.93	(14.1 – 89.3)
Neighborhood Poverty, Percentage <sup>a</sup>	18.08±11.90	(1.6 – 60.4)
<b>Inflammatory Biomarkers</b>		
TNF-α, pg/mL	12.2±3.8	(5.5 – 28.6)
IL-6, pg/mL	8.8±11.8	(0.9 – 73.1)
IL-8, pg/mL	16.4±5.9	(6.6 – 35.7)
IFN-γ, pg/mL	1.1±1.1	(0.1 – 6.1)
<b>COPD Outcomes</b>		
CAT	18.67±7.60	(0.0 – 35.0)
mMRC	1.96±1.02	(0.0 – 4.0)
SGRQ	50.35±16.88	(18.0 – 87.8)
Severe Exacerbations (in the Last 3 Months), n (% yes)	6 (10.7%)	
Moderate Exacerbations (in the Last 3 Months), n (% yes)	7 (12.5%)	
Severe Exacerbations (in the last 3 Months), # Episodes	0.13±0.38	(0 – 2)
Moderate Exacerbations (in the last 3 Months), # Episodes	0.25±0.92	(0 – 6)

<sup>a</sup>Percentage of families living below the poverty line in census tract, U.S. Census ACS 2013-17

SD=standard deviation; FEV<sub>1</sub>%pred=forced expiratory volume in 1 second percentage predicted; TNF=tumor necrosis factor; IL=interleukin; IFN=interferon; COPD=chronic obstructive pulmonary disease; CAT=COPD Assessment Test; mMRC=modified Medical Research Council dyspnea scale; SGRQ=St George's Respiratory Disease Questionnaire

There was also a significant plasma EPA+DHA difference in IL-6 mean concentrations, with higher EPA+DHA plasma levels associated with reduced IL-6 (Table 2). For example, IL-6 mean concentrations were 14.3% lower for those with 1 SD higher plasma EPA+DHA (95% CI 1.2%, 25.7%;  $p=0.03$ ). However, other markers of inflammation (TNF-α, IL-8, and IFN-γ) did not show associations with plasma EPA+DHA (Table 2).

### **Association of Total Omega-3 and Isolated Eicosapentaenoic Acid, Docosahexaenoic Acid, Docosapentaenoic Acid, and α-Linolenic Acid With COPD Morbidity and Biomarkers**

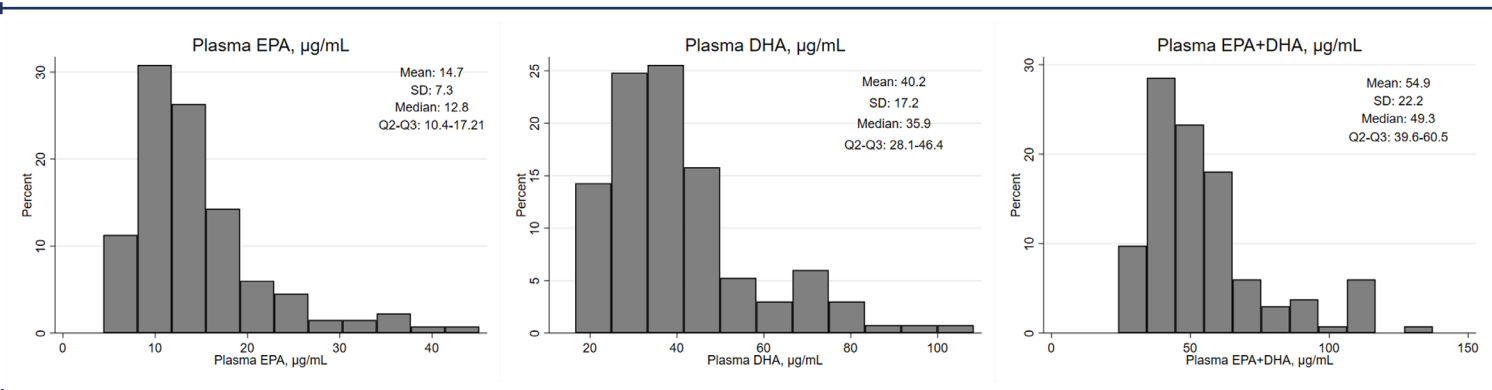
Associations between total omega-3 (EPA+DHA+DPA+ALA) and COPD outcomes were similar to those with EPA+DHA (Table 3). A higher total omega-3 level was associated with a 2.8-point lower SGRQ score (95% CI -5.3, -0.3;  $p=0.03$ ) and 60% lower odds of moderate exacerbations (CI 0.2, 0.97;  $p=0.04$ ). The results seem to be primarily driven by DHA, as a 1 SD increase (~17.2μg/mL) in DHA levels was associated with a 3.1 lower SGRQ score (95% CI -6.0, -0.2;  $p=0.04$ ) and 70% lower odds of moderate exacerbations (95% CI 0.1, 0.8;  $p=0.02$ ). DPA also demonstrated notable associations with these outcomes ([SGRQ; mean difference -2.3; 95% CI -4.7, 0.05,  $p=0.06$ ], [moderate exacerbations;

OR 0.4; 95% CI 0.2, 0.97,  $p=0.04$ ]) (Table 3). There was no association between EPA or ALA with COPD outcomes. There was no association between omega-3 fatty acids and respiratory outcomes when expressed as a percentage of total fatty acids (data not shown).

The patterns of associations between total omega-3 (EPA+DHA+DPA+ALA) and inflammatory biomarkers were similar to those shown with EPA+DHA. Adjusting for covariates, a higher total omega-3 level was associated with a 15.5% lower IL-6 concentration (95% CI 3.3%, 26.1%;  $p=0.01$ ), with DHA and DPA suggested as the primary drivers of the association. For example, a 1 SD increase in DHA levels was associated with a 16.1% lower IL-6 concentration (95% CI 2.7%, 27.7%;  $p=0.02$ ) and a 1 SD increase in DPA with a 14.9% lower IL-6 concentration (95% CI 2.5%, 25.7%;  $p=0.02$ ); however, IL-6 concentrations did not differ by either EPA or ALA. Other inflammatory biomarkers—TNF-α, IL-8, and IFN-γ—did not show associations with either total or individual plasma omega-3; and, when expressed as a percentage of total fatty acids, omega-3 fatty acids did not show associations with any inflammatory biomarkers, including IL-6 (data not shown).

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**Figure 1. Participants' Distribution of Eicosapentaenoic Acid and Docosahexaenoic Acid Plasma Levels**



EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid

**Table 2. Effect Estimates of Plasma Eicosapentaenoic Acid+Docosahexaenoic Acid (Per 1 Standard Deviation Increase) on COPD Outcomes and Biomarkers**

	Plasma EPA+DPA	
	Mean Difference (95% CI)	P-value
<b>CAT</b>	-0.8 (-2.4, 0.8)	0.32
<b>mMRC</b>	0.03 (-0.2, 0.2)	0.72
<b>SGRQ</b>	-2.7 (-5.2, -0.2)	0.04
<b>Exacerbations</b>	<b>Odds Ratio (95% CI)</b>	
Severe <sup>a</sup> (OR)	0.7 (0.3, 1.4)	0.32
Moderate <sup>b</sup> (OR)	0.4 (0.2, 0.9)	0.02
<b>Inflammatory Biomarkers</b>	<b>Percentage Difference in Geometric Mean Concentrations (95% CI)</b>	
TNF-α	-1.3% (-6.4%, 4.1%)	0.64
IL-6	-14.3% (-25.7%, -1.2%)	0.03
IL-8	1.0% (-7.3%, 10.1%)	0.81
IFN-γ	-2.1% (-16.5%, 14.7%)	0.79

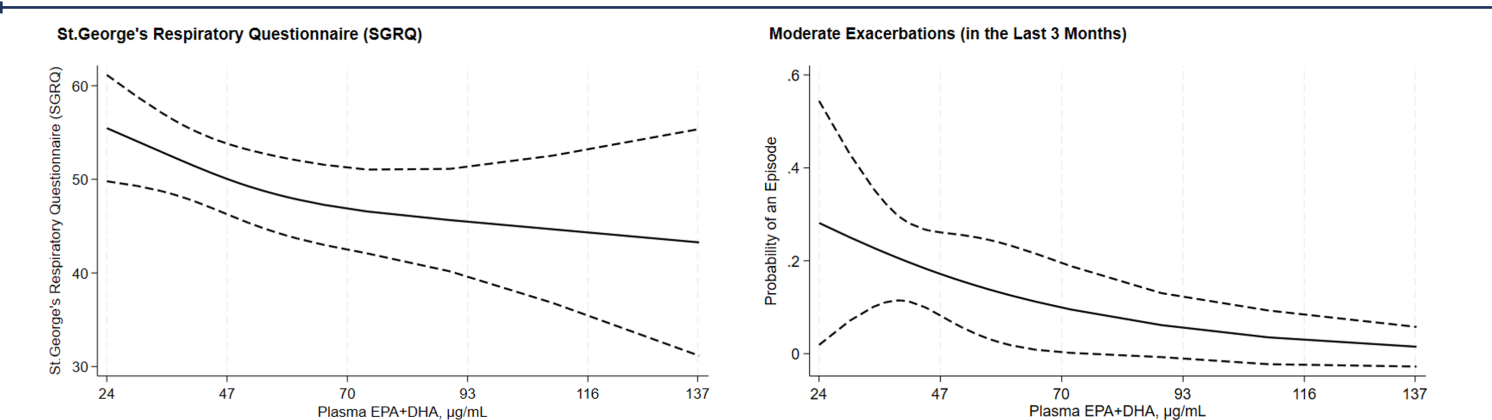
<sup>a</sup>Severe: ER/Hospital visits due to COPD in the last 3 months

<sup>b</sup>Moderate: Oral steroid use, antibiotic use, or unscheduled physician visit due to COPD in the last 3 months

Generalized linear mixed model regression of the repeated measures of COPD outcomes and biomarkers was run on the repeated measures of plasma omega 3. Adjusted by age, gender, race, education, pack years, comorbidity, BMI, FEV<sub>1</sub>%pred (GLI), and neighborhood poverty. For exacerbation outcomes only, the effect size is shown for plasma EPA+DHA increase of 22.1 µg/mL, which is slightly less than 1 standard deviation (22.2 µg/mL). The discrepancy is due to regression analyses for exacerbations having 1 fewer observation (N=132) than do for all other analyses (N=133).

COPD=chronic obstructive pulmonary disease; CI=confidence interval; CAT=COPD Assessment Test; mMRC=modified Medical Research Council dyspnea scale; SGRQ=St George's Respiratory Disease Questionnaire; OR=odds ratio; TNF=tumor necrosis factor; IL=interleukin; IFN=interferon BMI=body mass index; FEV<sub>1</sub> %pred=forced expiratory volume in 1 second percentage predicted; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid

**Figure 2. Predicted Levels of COPD Morbidity Across Plasma Eicosapentaenoic Acid +Docosahexaenoic Acid**



SGRQ=St George's Respiratory Disease Questionnaire; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid

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## Discussion

This study found that among former smokers with moderate-to-severe COPD, higher plasma omega-3 (EPA+DHA) levels were associated with lower COPD morbidity, specifically better respiratory-specific quality of life and reduced odds of moderate exacerbations. When exploring the association of individual fatty acids with respiratory morbidity, significant associations were particularly noted for DHA and, to a lesser extent, with DPA, as opposed to other measured fatty acids (EPA and ALA). Higher plasma omega-3 (EPA+DHA) levels were also associated with lower IL-6 concentrations, a common marker of systemic inflammation. This study utilizes objectively measured omega-3 levels to add to the emerging evidence about the potential role of diet in lung health and systemic inflammation.

Previous investigations into omega-3 PUFAs' effects on COPD morbidity have primarily relied on subjective measurements based on self-reported dietary intake.<sup>13-15,29</sup> Although widely adopted for use in epidemiological studies,<sup>30-32</sup> there are notable limitations to participant-reported dietary intake. Dietary intake surveys, by design, are instruments for categorizing participants based on previous dietary intake rather than estimating absolute nutritional intake<sup>33</sup> and are subject to reproducibility errors<sup>34</sup> and participant bias.<sup>35</sup> Previous studies utilizing self-reported dietary intake using food frequency questionnaires suggest that increased dietary intake of omega-3 fatty acids is linked with improved respiratory health, and in particular, lower incidence of bronchitis and emphysema,<sup>13</sup> better respiratory-specific quality of life,<sup>14</sup> lower odds of respiratory symptoms,<sup>15</sup> higher lung function,<sup>13</sup> and lower concentrations of serum inflammatory markers.<sup>29</sup> Moreover, emerging data indicates that the positive impact of omega-3 consumption on respiratory health may be particularly noteworthy in individuals exposed to deleterious environmental factors like cigarette smoke exposure,<sup>15</sup> thereby, contributing additional evidence to underscore the significance of omega-3 PUFAs in influencing COPD health outcomes.

By utilizing objective plasma markers of omega-3 PUFAs, our findings contribute valuable insights into the potentiation of supplements and dietary modifications to regulate the effects of specialized proresolving mediators (SPMs) for combating respiratory health decline in moderate-to-severe COPD patients. Furthermore, our study illuminates DHA as a potential target for therapeutic intervention in promoting respiratory protection. Higher plasma omega-3 levels were associated with better respiratory-specific quality of life and reduced moderate exacerbation risk. It is noteworthy that a 1 SD higher EPA/DHA was associated with a 2.7 lower score in SGRQ, a difference that approaches but does not reach the minimum clinically important difference for the SGRQ, which is generally regarded as 4 points.<sup>36</sup>

However, many clinical trials of approved medications for COPD<sup>37,38</sup> similarly show a ~2.7 difference in SGRQ score. In addition, a larger increase in omega-3 (EPA/DHA), such as 32.9µg/mL or higher, may be required to have a clinically significant change in SGRQ (>4 points). In our cohort, such a large difference in omega-3 is shown when comparing the participants, for example, with the 10th and 90th percentile levels of omega-3; the bottom 10% of our sample had plasma EPA+DHA levels below 34.9µg/mL while the top 10% were at or above 88.9µg/mL, for a difference of 54.5µg/mL, which would be commensurate with ~6.6 point difference in predicted SGRQ scores.

Omega-3 fatty acids may play a role in airway inflammation of COPD. SPMs, which encompass resolvins, protectins, and maresins, are biosynthesized from EPA and DHA fatty acids and have been shown to regulate and promote the resolution of deleterious inflammation.<sup>8</sup> SPMs' homeostatic promotive actions are the result of their stimulation of macrophage phagocytosis of apoptotic cells, cellular debris, and microbes, cessation of superfluous neutrophils (PMN) infiltration, and counter-regulation of pro-inflammatory chemokines and cytokines.<sup>39</sup> Maresin-1 (MaR1), a member of the SPM family derived from polyunsaturated fatty acids, specifically DHA, stands out for its potent anti-inflammatory properties in the airway.<sup>40</sup> MaR1 exerts inhibitory effects on specific isoforms of protein kinase C (PKC), such as PKCα and PKCε, which are crucial components of the signaling cascade leading to the release of proinflammatory cytokines like TNF-α, IL-6, and IL-8, thereby, effectively reducing their activation.<sup>41</sup> Additionally, MaR1 actively promotes the transition of macrophages from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype, furthering SPMs' multifaceted role in resolving inflammation.<sup>40</sup> In support of a potentially anti-inflammatory mechanism of action, omega-3 intake, particularly DHA, was associated with lower IL-6 levels in the current study.

As noted, significant associations were found primarily for DHA, and to a lesser extent DPA, when analyzing fatty acids separately. These findings are similar to those found in the study by Patchen et al, which also showed that plasma DHA was associated with attenuation of lung function decline and reduced incidence of airway obstruction.<sup>17</sup> Evidence suggests that DHA may signal a reduction in the speed of EPA's metabolic processes, modifying its entry into its metabolic pathway and thereby, potentially reducing the production of downstream anti-inflammatory SPMs.<sup>42</sup> However, these DHA and EPA competitive mechanisms, inhibitive processes, and associated effects have yet to be well understood but may explain DHA's potent respiratory protective effects compared to EPA.

While our study provided valuable insights into the relationship between plasma omega-3 levels and COPD

**Table 3. Effect Estimates of Plasma Eicosapentaenoic Acid, Docosahexaenoic Acid,  $\alpha$ -Linolenic Acid, and Docosapentaenoic Acid (Per 1 Standard Deviation Increase) on COPD Outcomes**

	P-value		P-value	
	Plasma EPA (20:5n-3)		Plasma DHA (22:6n-3)	
	Mean Difference (95% CI)		Mean Difference (95% CI)	
CAT	-0.2 (-1.6, 1.2)	0.77	-1.0 (-2.7, 0.7)	0.24
mMRC	0.01 (-0.2, 0.2)	0.93	0.04 (-0.2, 0.2)	0.68
SGRQ	-0.9 (-3.0, 1.2)	0.40	-3.1 (-6.0, -0.2)	0.04
<b>Exacerbations</b>	<b>Odds Ratio (95% CI)</b>		<b>Odds Ratio (95% CI)</b>	
Severe <sup>a</sup> (OR)	0.8 (0.4, 1.6)	0.61	0.7 (0.3, 1.5)	0.37
Moderate <sup>b</sup> (OR)	0.7 (0.4, 1.4)	0.30	0.3 (0.1, 0.8)	0.02
	Plasma DPA (22:5n-3)		Plasma ALA (18:3n-3)	
	Mean Difference (95% CI)		Mean Difference (95% CI)	
CAT	-0.5 (-1.8, 0.4)	0.40	-0.7 (-1.8, 0.4)	
mMRC	-0.004 (-0.2, 0.1)	0.96	-0.1 (-0.2, 0.1)	0.23
SGRQ	-2.3 (-4.7, 0.05)	0.06	-1.4 (-3.7, 0.9)	0.49
<b>Exacerbations</b>	<b>Odds Ratio (95% CI)</b>		<b>Odds Ratio (95% CI)</b>	0.24
Severe <sup>a</sup> (OR)	0.9 (0.5, 1.5)	0.60	1.4 (0.8, 2.6)	
Moderate <sup>b</sup> (OR)	0.4 (0.2, 0.97)	0.04	0.8 (0.4, 1.9)	0.26
	Plasma EPA+DHA+DPA+ALA		0.68	
	Mean Difference (95% CI)			
CAT	-0.9 (-2.3, 0.5)			
mMRC	-0.04 (-0.2, 0.1)	0.21		
SGRQ	-2.8 (-5.3, -0.3)	0.61		
<b>Exacerbations</b>	<b>Odds Ratio (95% CI)</b>	0.03		
Severe <sup>a</sup> (OR)	0.9 (0.4, 1.6)			
Moderate <sup>b</sup> (OR)	0.4 (0.2, 0.97)	0.68		

<sup>a</sup>Severe: ER/hospital visits due to COPD in the last 3 months

<sup>b</sup>Moderate: Oral steroid use, antibiotic use, or unscheduled physician visit due to COPD in the last 3 months

Generalized linear mixed model regression of the repeated measures of COPD outcomes was run on the repeated measures of plasma omega 3. Adjusted by age, gender, race, education, pack years, comorbidity, BMI, FEV<sub>1</sub>%pred (GLI), and neighborhood poverty. For exacerbations outcomes only, the effect size is shown for plasma EPA+DHA increase of 22.1 $\mu$ g/mL, which is slightly less than 1 standard deviation (22.2 $\mu$ g/mL). The discrepancy is due to regression analyses for exacerbation outcomes having one fewer observation (N=132) than do for all other analyses (N=133). Similarly, for exacerbation outcomes only, the effect estimates for plasma EPA alone, DHA alone, DPA alone, ALA alone, and EPA+DHA+DPA+ALA were based on 7.3 $\mu$ g/mL, 17.0 $\mu$ g/mL, 3.9 $\mu$ g/mL, 6.9 $\mu$ g/mL, and 25.7 $\mu$ g/mL increases in the fatty acid respectively, which were slightly different - in decimal point range - to 1 standard deviation of each fatty acid (7.3 $\mu$ g/mL, 17.2 $\mu$ g/mL, 3.9 $\mu$ g/mL, 6.9 $\mu$ g/mL, and 25.8 $\mu$ g/mL).

COPD=chronic obstructive pulmonary disease; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid; CI=confidence interval; CAT=COPD Assessment Test; mMRC=modified Medical Research Council dyspnea scale; SGRQ=St George's Respiratory Disease Questionnaire; OR=odds ratio; DPA=docosapentaenoic acid; ALA= $\alpha$ -linolenic acid; BMI=body mass index; FEV<sub>1</sub> %pred=forced expiratory volume in 1 second percentage predicted

morbidity, our study had several notable limitations. Given the seasonal and individual variability in COPD exacerbations, a more extended follow-up period, ideally 12 months or longer, would have been ideal to account for these variables. The sample size was relatively small; however, the longitudinal design (multiple visits per participant) allowed a more robust examination of the associations and gained power. Still, the power was inadequate for several outcomes, including severe exacerbation risk. It is possible that we would have identified additional statistically significant associations with a larger sample size. Our results highlight the need for more extensive studies to fully understand the potential link between omega-3 fatty acids and COPD morbidity. The study did not collect information on whether participants were taking supplementation for omega-3. Hence, the potentially differing role of natural diet versus supplementation on plasma omega-3-COPD morbidity relationship could not be examined. Also, residual confounding could not be ruled

out as this study was observational; however, in an attempt to rule out the confounding issue as much as possible, this study included several demographic and COPD-related risk factors, including the indicators of individual and neighborhood socioeconomic status, smoking pack years, BMI, comorbidities, and spirometry-measured lung function at baseline. Still, there are other possible confounding variables, such as whether high omega-3 levels reflect better health care or patient adherence, and unmeasured confounders make it challenging to assign causality and point to a need for randomized controlled trials to better elucidate causal relationships. Previously conducted studies in the United States, which assessed participants' plasma EPA+DHA, reported mean values (55.6–60.8 $\mu$ g/mL)<sup>9,43</sup> that were in alignment with our study's sample population (54.02 $\mu$ g/mL). However, it is essential to acknowledge that our study's findings may have limited generalizability for individuals with moderate-to-severe COPD who are current

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smokers or have higher incomes.

In conclusion, our findings suggest that higher plasma EPA, DHA, and DPA levels in isolation are associated with better respiratory-specific quality of life and lower odds of moderate exacerbations in former smokers with moderate-to-severe COPD. These findings underscore the potential therapeutic benefits of a diet rich in omega-3 fatty acids and lay the groundwork for future prospective clinical trials to investigate the efficacy of such dietary interventions in managing COPD-related morbidities.

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**Author contributions:** HW and NNH were responsible for the concept, design, analysis, and interpretation of data.

TAK and NNH were responsible for drafting the manuscript. All authors contributed to data analysis, drafting, revision, and final approval of the version submitted for publication and agree to be accountable for all aspects of the work.

### **Declaration of Interest**

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