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Omega-3 polyunsaturated fatty acids and the psychiatric post-acute sequelae of COVID-19: A one-year retrospective cohort analysis of 33,908 patients

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ABSTRACT

Background: Early prevention and management of psychiatric symptoms in long COVID (or post-COVID-19 conditions) are crucial for reducing long-term disability. Existing clinical guidelines recommend the use of omega-3 polyunsaturated fatty acids (PUFAs) as a promising therapeutic approach for various common psychiatric disorders due to their anti-inflammatory and neuroprotective characteristics. This study aims to investigate the potential efficacy of omega-3 PUFAs in alleviating the psychiatric sequelae following COVID-19.

Methods: This 1-year retrospective cohort study used the TriNetX electronic health records network to examine the effects of omega-3 PUFAs supplements on psychiatric sequelae in adults diagnosed with COVID-19. Using propensity-score matching, the study compared those who used omega-3 PUFAs supplements with those who did not, assessing outcomes including depression, anxiety disorders, insomnia, and other somatic conditions up to a year after COVID-19 diagnosis.

Results: In 16,962 patients who received omega-3 PUFAs supplements and 2,248,803 who did not, omega-3 supplementation significantly reduced the risk of developing psychiatric sequelae post-COVID-19 diagnosis (HR, 0.804; 95% CI, 0.729 to 0.888). Specifically, the risks for depression (HR, 0.828; 95% CI, 0.714 to 0.960), anxiety disorders (HR, 0.833; 95% CI, 0.743 to 0.933), and insomnia (HR, 0.679; 95% CI, 0.531 to 0.869) were reduced in the omega-3 group. This effect was consistent across sex, race, 18–59 age group, and patients with less than two doses of the COVID-19 vaccine. The omega-3 group also had a lower risk of cough and myalgia, but no significant difference was noted for other symptoms like chest pain, abnormal breathing, abdominal issues, fatigue, headache, and cognitive symptoms.

Conclusion: Omega-3 PUFAs may require re-evaluation as a preventive strategy against adverse mental health outcomes post-COVID-19 in placebo-controlled clinical trials.

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1. Introduction

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, millions of confirmed cases and fatalities have been reported worldwide (WHO, 2021). Following recovery from the acute phase of COVID-19, individuals often experience persistent health issues, collectively known as "long COVID" or "post-COVID-19 condition." (Daugherty et al., 2021; Lai et al., 2022b; Peter et al., 2022). This condition affects individuals across disease severities and manifests as diverse symptoms (Duncan et al., 2020), including fatigue, shortness of breath, cognitive dysfunction, and the common psychiatric sequelae ofanxiety, depression, and insomnia (Al-Aly et al., 2021; Taquet et al., 2021). Early recognition, prevention, and management of the high incidence of mental health outcomes are crucial as they contribute to long-term disability in individuals with post-COVID-19 condition (Al-Aly et al., 2021; Schou et al., 2021; Taquet et al., 2021). However, evidence-based prevention or treatment strategies for post-COVID-19 neuropsychiatric conditions are currently lacking.

Chronic inflammation stemming from a potent immune response to SARS-CoV-2 has been linked to neuropsychiatric manifestations observed in post-COVID-19 conditions (Fajgenbaum and June 2020; Lai et al., 2022a; Liang et al., 2022; Liu et al., 2023a; Mazza et al., 2020; Yang et al., 2022). Preliminary guidelines have been emerging for diagnosing and managing long COVID (Crook et al., 2021; Shah et al., 2021; Yelin et al., 2022), and interest is growing in the potential role of anti-inflammatory nutritional or lifestyle interventions. Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA), have been investigated extensively for its biological mechanisms of mitigating inflammation, oxidative stress and coagulopathy (Calder et al., 2020; Chang et al., 2020b; Yang et al., 2022), and have shown promise in inflammation-related neuropsychiatric disorders in numerous clinical trials (Chang et al., 2020a; Keshavarz et al., 2018; Mazereeuw et al., 2016; Sinn et al., 2012; Su et al., 2014). Existing guidelines, such as the International Society for Nutritional Psychiatry Research (ISNPR) practice guidelines for the use of omega-3 PUFAs in treating major depressive disorder (MDD) (Guu et al., 2019), may provide insights for post-COVID-19 care. However, there is a notable lack of clinical studies investigating the role of omega-3 PUFAs in post-COVID-19 neuropsychiatric conditions.

To address this research gap, we conducted a retrospective cohort study using the TriNetX, a global health research network that provides comprehensive, up-to-date, and longitudinal patient data from healthcare organizations. Our study focused on assessing the efficacy of omega-3 PUFAs in preventing the psychiatric sequelae of COVID-19 and other post-COVID-19 conditions.

2. Methods

2.1. Data source

This study used data from the TriNetX Research Network, a collaborative health research platform that aggregates de-identified patient-level data from electronic health records, including demographic data, diagnoses, procedures, medications, laboratory data, genomic data, and types of healthcare organization (HCO) visits (TriNetX, n.d.). The TriNetX contains data from over 120 HCOs globally, typically academic health centers that collect data from their affiliated facilities, including main and satellite hospitals and outpatient clinics. For this analysis, we used the Research Network, which contains the data of over 107 million patients from 80 HCOs. The TriNetX platform includes built-in tools for analyzing patient-level data, and the results are provided to researchers in an aggregate form. Detailed information on the database can be found online. Written informed consent was not required because The TriNetX contains anonymized data. The Institutional Review Board of the Chi Mei Medical Center approved the study protocol (no. 11202-002).

2.2. Patient selection

The study population was drawn from a dataset dated May 7, 2023, from the TriNetX Research Network. The patient cohort was created from non-hospitalized individuals aged ≥18 years who tested positive for SARS-CoV-2 infection or were diagnosed with COVID-19 between March 1, 2020, and July 1, 2022, and had at least two medical encounters with Health Care Organizations (HCOs) during this period. Patients who used omega-3 PUFAs supplements within six months prior to their COVID-19 diagnosis were classified as the omega-3 group, while those who did not use omega-3 PUFAs supplements 6 months prior to or within 6 months after their diagnosis were categorized as the non-omega-3 group. To accurately attribute post-COVID-19 symptoms, we used different timeframes for the omega-3 group and the non-omega-3 group. This was done to ensure that individuals in the omega-3 group had started taking omega-3 supplements before being diagnosed with COVID-19, rather than after the onset of the disease. Our concern was that some people might start taking omega-3 supplements only after experiencing post-COVID-19 symptoms, which could introduce misclassification bias.

In the next stage of selection, we excluded patients from both groups who were prescribed COVID-19 antiviral agents (remdesivir, molnupiravir, nirmatrelvir and ritonavir), those who required initial hospitalization, those diagnosed with disorders of lipoprotein metabolism, hypertensive diseases, ischemic heart diseases, and type 2 diabetes mellitus (T2DM). We also excluded patients who died within one year after the index date and those diagnosed with post-COVID-19 related symptoms three months prior to the index date. Our rationale for excluding patients using antiviral medication was rooted in our focus on identifying patients with mild symptoms with low risk of developing severe COVID-19. This decision is based on the fact that patients with mild symptoms represents the majority of cases. Importantly, prior studies have revealed that post-COVID-19 conditions affect individuals with mild symptoms and those who were not hospitalized, not solely restricted to severe cases (Duncan et al., 2020). This strategy aligns with the National Institutes of Health COVID-19 Treatment Guidelines. As outlined in the guidelines, antiviral medications such as ritonavir, nirmatrelvir, and molnupiravir are recommended for adults with mild to moderate COVID-19 who are at a high risk of progressing to severe illness. Similarly, Remdesivir is indicated for hospitalized patients at a high risk of progressing to severe COVID-19 or requiring minimal conventional oxygen support. Given these considerations, these patients using antiviral agents are not our target population.

After application of these criteria, we conducted 1:1 propensity score matching by age at the index date, race, gender, adverse socioeconomic determinants of health, and comorbid medical conditions for the remaining patients in the omega-3 and non-omega-3 groups. Further details about the inclusion and exclusion criteria and additional patient information can be found in Supplementary Appendix Table S1 & S2.

2.3. Covariates

We considered 32 variables to adjust for imbalances in baseline characteristics between the omega-3 and non-omega-3 groups. We used a list of both confirmed and suspected risk factors for COVID-19 and more severe cases of the illness (Liu et al., 2023b; Taquet et al., 2021; Wang et al., 2022). These covariates encompassed demographic characteristics, socioeconomic determinants, and various comorbidities. Demographic characteristics were delineated by age at index, sex (female or male), race (White, Black or African American, Asian, or Unknown Race), and ethnicity (Hispanic or Latino, Not Hispanic or Latino, or Unknown Ethnicity). Socioeconomic determinants of health included considerations of challenges related to housing and economic circumstances. A range of comorbidities was considered, including overweight and obesity, neoplasms, nicotine dependence, substance use disorders, cerebral infarction, chronic kidney disease, chronic lower respiratory

diseases such as chronic obstructive pulmonary disease and emphysema, asthma, fatty liver, liver fibrosis, liver cirrhosis, chronic hepatitis, and alcoholic liver disease. Immune disorders such as immunodeficiency with predominantly antibody defects, human immunodeficiency virus disease, sarcoidosis, psoriasis, systemic lupus erythematosus, and rheumatoid arthritis were also considered.

A wide range of comorbidities was also accounted for, such as overweight and obesity, neoplasms, nicotine dependence, substance use disorders, and cerebral infarction. It also considered chronic health conditions, including chronic kidney disease (CKD), chronic lower respiratory diseases (including chronic obstructive pulmonary disease, emphysema, and asthma), and chronic liver diseases (which include fatty liver, fibrosis and cirrhosis of the liver, chronic hepatitis, and alcoholic liver disease). Immune disorders like immunodeficiency with predominantly antibody defects, human immunodeficiency virus disease, sarcoidosis, psoriasis, systemic lupus erythematosus, and rheumatoid arthritis were also included in the analysis. A standard difference of less than 0.1 indicates good matching (Haukoos and Lewis, 2015).

2.4. Outcomes

Outcomes were identified through International Classification of Diseases, Tenth Revision codes (ICD-10). The primary outcome was the incidence of specific psychiatric sequela within a 90-day to one-year period post COVID-19 diagnosis. The specific psychiatric sequelae include anxiety (F41, F43.25, F43.24, F43.22, F43.23), depression (F32, F31.4, F31.5, F34.1, F31.31, F31.32, F31.75, F31.76, F43.219, F33.0, F33.1, F33.2, F33.3, F33.9), and insomnia (G47.0). Secondary outcomes encompassed other post-COVID-19 common neuropsychiatric and somatic conditions, including chest/throat pain, abnormal breathing, abdominal symptoms, fatigue, headache, myalgia, loss of taste/smell, cough, palpitation, and cognitive symptoms. These variables and their corresponding ICD codes are comprehensively detailed in Table S3.

2.5. Statistical analysis

All statistical analyses were conducted using the TriNetX platform. The baseline characteristics of the study cohorts are described in terms of the mean, standard deviation, or proportion, whichever is most appropriate. Propensity score matching at a 1:1 ratio was conducted using the built-in function of the TriNetX network (TriNetX, n.d.). The TriNetX platform uses input matrices of user-identified covariates to perform logistic regression analysis of all individual subjects using propensity matching scores. Patients are matched based on the greedy nearest-neighbor algorithm, with a caliper width of 0.1 pooled standard deviations. The algorithm's "greedy" approach ensures local decision-making, effectively minimizing differences in propensity scores. This process aims to reduce bias and enhance comparability between the omega-3 and non-omega-3 groups, contributing to a more robust evaluation of omega-3's impact on post COVID-19 condition. We assessed the balance between the two cohorts using standardized difference. Differences of absolute value > 0.1 are considered to indicate significant residual imbalance (Haukoos and Lewis, 2015).

The survival analysis was performed by plotting Kaplan-Meier curves with log-rank tests and calculating hazard ratio (HR) to compare the 2 groups. All analyses were conducted using a 95% confidence interval (CI) to determine statistical significance. Statistical significance was indicated at p value < 0.05. The effect of omega-3 on the risk of psychiatric sequelae of COVID-19 was further examined within prespecified subgroups by age (18–59, and $\geq$60 years), sex, vaccination status and race.

3. Results

3.1. Patient characteristics

Between March 1, 2020, and July 1, 2022, 16,962 patients with omega-3 PUFAs supplements were identified, and 2,248,803 patients without omega-3 PUFAs supplementation were subjected to matching (Fig. 1).

Table 1 summarizes the baseline characteristics of the omega-3 and non-omega groups, before and after propensity score matching. Prior to matching, the omega-3 and non-omega-3 groups demonstrated notable disparities. Specifically, the mean age of the omega-3 group was older, at 46.6 $\pm$ 18.1 years, compared to 41.9 $\pm$ 16.9 years in the non-omega-3 group. In terms of race, the omega-3 cohort had a significantly higher proportion of white individuals, constituting 67% of the group, whereas they represented 45% of the non-omega-3 group. Ethnicity distribution also differed between the two groups prior to matching. The non-omega-3 group had a higher prevalence of individuals who were not Hispanic or Latino, at 45%, compared to 30% in the omega-3 group. Regarding comorbidities, before matching, conditions like nicotine dependence and substance use disorders were more common in the omega-3 group. However, after conducting propensity score matching, these differences were largely rectified. The absolute standardized mean differences between the two groups for all variables became less than 0.1. This indicated a high level of balance between the omega-3 and non-omega-3 groups, enhancing the validity of the comparative analyses.

3.2. Primary outcomes

During the follow-up period of 90 days to one year, 633 patients in the omega-3 group developed psychiatric sequelae of COVID-19, while 1,048 patients in the non-omega-3 group developed this condition (Table 2). The risk of developing psychiatric sequelae of COVID-19 was significantly lower in the omega-3 group when compared to the non-omega-3 group (HR, 0.804; 95% CI, 0.729 to 0.888).

Fig. 2 depicts the Kaplan-Meier survival curves representing the probability of any psychiatric sequelae subsequent to COVID-19. Patients within the omega-3 group exhibited a significantly lower risk of developing psychiatric sequelae when compared to patients who did not receive omega-3 supplementation. This difference in outcome probabilities between the two groups was confirmed statistically significant using the log-rank test, yielding a p-value of less than 0.001.

3.3. Secondary outcomes

In the psychiatric sequelae, patients in the omega-3 group demonstrated a significantly reduced risk of developing depression (HR, 0.828; 95% CI, 0.714 to 0.960), anxiety disorders (HR, 0.833; 95% CI, 0.743 to 0.933) and insomnia (HR, 0.679; 95% CI, 0.531 to 0.869) compared to the non-omega-3 group (Table 2 and Fig. 3).

Regarding other post-COVID-19 conditions, our study observed a lower risk in the omega-3 group compared to the non-omega-3 group for conditions such as cough (HR, 0.814; 95% CI, 0.683 to 0.970) and myalgia (HR, 0.606; 95% CI, 0.417 to 0.880) (Table 3). However, there was no significant difference between the two groups in terms of chest/throat pain (HR, 1.126; 95% CI, 0.942 to 1.345), abnormal breathing (HR, 1.110; 95% CI, 0.921 to 1.337), abdominal symptoms (HR, 1.021; 95% CI, 0.905 to 1.151), fatigue (HR, 0.937; 95% CI, 0.784 to 1.119), headache (HR, 0.864; 95% CI, 0.730 to 1.023), loss of taste/smell (HR, 0.450; 95% CI, 0.091 to 2.231), palpitation (HR, 0.807; 95% CI, 0.578 to 1.127), and cognitive symptoms (HR, 1.195; 95% CI, 0.768 to 1.859).

3.4. Subgroup analyses

Subgroup analyses by sex, age, race, and vaccination status were conducted. Compared with the non-omega-3 group, the omega-3 group

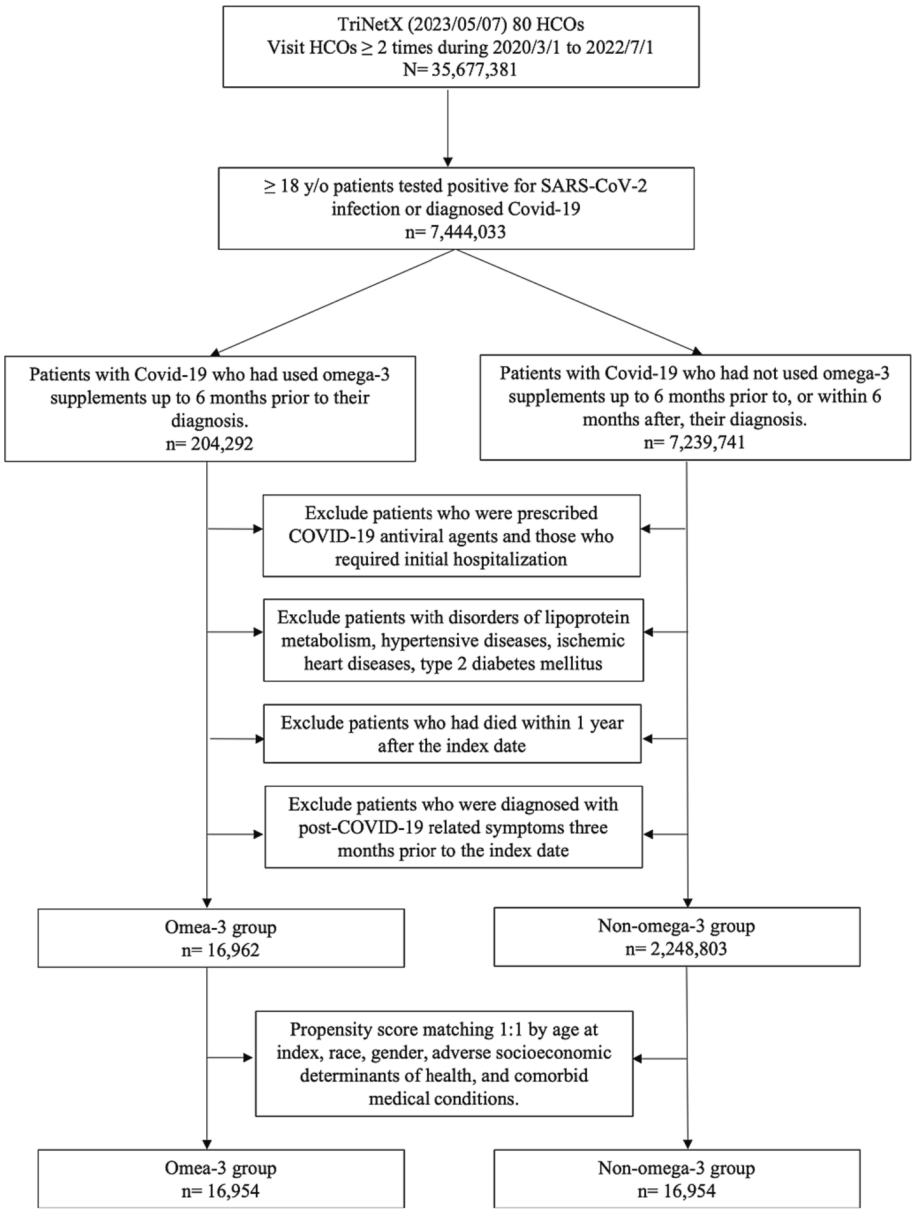

Fig. 1. The algorithm of patient selection and cohort construction.

had significantly and consistently lower HR for the primary composite outcome in most subgroups (Fig. 4), including male (HR, 0.697; 95% CI, 0.559 to 0.868), female (HR, 0.879; 95% CI, 0.786 to 0.984), age 18 –59 (HR, 0.765; 95% CI, 0.688 to 0.85), patients vaccinated less than 2 doses (HR, 0.769; 95% CI, 0.695 to 0.851), white (HR, 0.832; 95% CI, 0.743 to 0.932) and non-white patients (HR, 0.705; 95% CI, 0.547 to 0.909).

In regard to the psychiatric sequela depict in Fig. 5, the omega-3 group displayed a lower risk of depression compared to the non-omega-3 group in most subgroups, with the exception of the ≥60 age group, patients vaccinated ≥2 doses, and both white and non-white groups. In terms of anxiety, the omega-3 group had a lower risk compared to the non-omega-3 group in most subgroups, except for female participants, those in the ≥60 age group, and patients who received ≥2 doses of the vaccine. Finally, when it comes to insomnia, the omega-3 group had a lower risk compared to the non-omega-3 group in most subgroups, except for male participants, those in the ≥60 age group, patients who received ≥2 doses of the vaccine, and the non-white group.

In regard to other post-COVID-19 conditions (as illustrated in Figs. S1, S2, S3, S4), there were mostly no significant differences observed across all subgroups. However, there were a few exceptions to this general trend. For instance, in the age group of 60 and above, there was a significantly lower risk of developing a cough in the omega-3 group compared to the non-omega-3 group. Furthermore, a significantly lower risk of headache was observed in the omega-3 group compared to the non-omega-3 group for both males and females as well as in the non-white racial group. Similarly, a significantly lower risk of myalgia was found in the omega-3 group compared to the non-omega-3 group for females and the non-white racial group. Additionally, in patients who received less than two doses of the vaccine, a significantly lower risk was observed in the omega-3 group for headache, myalgia, cough, and palpitation.

4. Discussion

To our knowledge, this is the first study to investigate the efficacy of omega-3 PUFAs in neuropsychiatric sequelae of COVID-19 and other post-COVID-19 conditions. Our main finding is that patients who

Table 1
Comparison of characteristics of patients with Omega-3and Non-omega-3 groups before and after matching.

	Before matching			After matching		
	Omega-3 group (n = 16,962)	Non-omega-3 group (n = 5,260,322)	Std diff	Omega-3 group (n = 16,954)	Non-omega-3 group (n = 16,954)	Std diff
Age at Index	46.6 ± 18.1	41.9 ± 16.9	<0.001	46.6 ± 18.1	46.6 ± 18.1	<0.001
Sex						
Female	10267 (60.53)	1395871 (62.07)	0.032	10263 (60.53)	10251 (60.46)	0.001
Male	6690 (39.44)	851919 (37.88)	0.032	6686 (39.44)	6699 (39.51)	0.002
Race						
White	11439 (67.44)	1004709 (44.68)	0.471	11438 (67.47)	11452 (67.55)	0.002
Black or African American	3890 (22.93)	182659 (8.12)	0.418	3883 (22.9)	3890 (22.94)	0.001
Asian	277 (1.63)	57147 (2.54)	0.064	277 (1.63)	283 (1.67)	0.003
Unknown Race	1266 (7.46)	996645 (44.32)	0.927	1266 (7.47)	1234 (7.28)	0.007
Ethnicity						
Hispanic or Latino	937 (5.52)	123633 (5.5)	0.001	937 (5.53)	965 (5.69)	0.007
Not Hispanic or Latino	5119 (30.18)	1004485 (44.67)	0.303	5119 (30.19)	5063 (29.86)	0.007
Unknown Ethnicity	10906 (64.3)	1120684 (49.84)	0.295	10898 (64.28)	10926 (64.45)	0.003
Socioeconomic determinants of health						
Problems related to housing and economic circumstances	104 (0.61)	3049 (0.14)	0.078	102 (0.6)	91 (0.54)	0.009
Problems related to education and literacy	10 (0.06)	852 (0.04)	0.010	10 (0.06)	10 (0.06)	<0.001
Problems related to employment and unemployment	18 (0.11)	1503 (0.07)	0.013	18 (0.11)	13 (0.08)	0.010
Comorbidities						
Overweight and obesity	631 (3.72)	71371 (3.17)	0.030	631 (3.72)	605 (3.57)	0.008
Neoplasms	1393 (8.21)	155503 (6.92)	0.049	1393 (8.22)	1340 (7.9)	0.011
Nicotine dependence	654 (3.86)	49018 (2.18)	0.098	650 (3.83)	625 (3.69)	0.008
Substance use disorders	1081 (6.37)	73291 (3.26)	0.146	1076 (6.35)	1045 (6.16)	0.008
Cerebral infarction	69 (0.41)	2296 (0.1)	0.061	64 (0.38)	46 (0.27)	0.019
Chronic kidney disease	96 (0.57)	4396 (0.2)	0.060	95 (0.56)	71 (0.42)	0.020
Chronic lower respiratory diseases						
Chronic obstructive pulmonary disease	629 (3.71)	86281 (3.84)	0.007	629 (3.71)	593 (3.5)	0.011
Emphysema	46 (0.27)	2420 (0.11)	0.038	46 (0.27)	29 (0.17)	0.021
Asthma	423 (2.49)	69443 (3.09)	0.036	423 (2.5)	433 (2.55)	0.004
Chronic liver diseases						
Fatty liver	105 (0.62)	7668 (0.34)	0.040	105 (0.62)	91 (0.54)	0.011
Fibrosis and cirrhosis of liver	73 (0.43)	3142 (0.14)	0.055	72 (0.43)	49 (0.29)	0.023
Chronic hepatitis	10 (0.06)	283 (0.01)	0.025	10 (0.06)	10 (0.06)	<0.001
Alcoholic liver disease	50 (0.3)	1403 (0.06)	0.055	49 (0.29)	33 (0.2)	0.019
Immune disorders						
Immunodeficiency with predominantly antibody defects	10 (0.06)	1059 (0.05)	0.005	10 (0.06)	10 (0.06)	<0.001
Human immunodeficiency virus disease	58 (0.34)	3330 (0.15)	0.039	58 (0.34)	41 (0.24)	0.019
Sarcoidosis	16 (0.09)	1444 (0.06)	0.011	16 (0.09)	19 (0.11)	0.006
Psoriasis	51 (0.3)	8307 (0.37)	0.012	51 (0.3)	95 (0.56)	0.040
Systemic lupus erythematosus	37 (0.22)	2754 (0.12)	0.023	37 (0.22)	37 (0.22)	<0.001
Rheumatoid arthritis	36 (0.21)	2848 (0.13)	0.021	36 (0.21)	39 (0.23)	0.004

Table 2
The hazard ratio and events number for comparing matched Omega-3and Non-omega-3 group for the primary composite outcome and its constituents.

Outcome	Number of patients with outcome		Hazard ratio	(95 %CI)	P value
	Omega-3 group n = 16,954	Non-omega-3 group n = 16,954			
Any post-acute psychiatric sequela	633	1,048	0.804	(0.729, 0.888)	<.001
Depression	284	459	0.828	(0.714, 0.960)	0.012
Anxiety	479	769	0.833	(0.743, 0.933)	0.002
Insomnia	95	189	0.679	(0.531, 0.869)	0.002

received omega-3 PUFA supplements prior to infection had a lower risk of experiencing psychiatric symptoms following COVID-19. Specifically, these patients were less likely to have depression, anxiety, and insomnia compared to those who did not receive omega-3 PUFAs supplements. It is worth noting that this protective effect was consistent across different demographic subgroups, including sex, race, and age group of 18–59, as well as patients who had received less than 2 doses of the COVID-19 vaccine. All together, these findings suggest that omega-3 PUFAs supplements may be a preventative measure for reducing the risk of psychiatric sequela in patients with COVID-19.

Although this study is the first to provide evidence for the potential benefits of omega-3 PUFAs in mitigating psychiatric sequelae following COVID-19, prior research has already established a beneficial effect of omega-3 PUFAs on mental health. Systematic reviews and meta-analyses discovered an overall beneficial impact of omega-3 PUFAs on depressive symptoms in patients diagnosed with major depressive disorder (Lin et al., 2012; Lin and Su, 2007; Mocking et al., 2016). Moreover, an expert consensus panel from the ISNPR endorsed the use of omega-3 PUFAs in treating major depressive disorders in specific populations, such as pregnant women, children, and the elderly, and also for preventive measures in high-risk individuals (Guu et al., 2019). Chronic inflammation is involved in the etiology of depression. Of particular relevance to this context, we have previously conducted a double-blind RCT to test the effects of omega-3 PUFA supplementation in the prevention of interferon-α-induced depression, and found that incident rates of interferon-α-induced depression were significantly reduced in EPA-treated patients. This study further confirms the notion that omega-3 PUFAs may be effective antidepressants in the context of depression

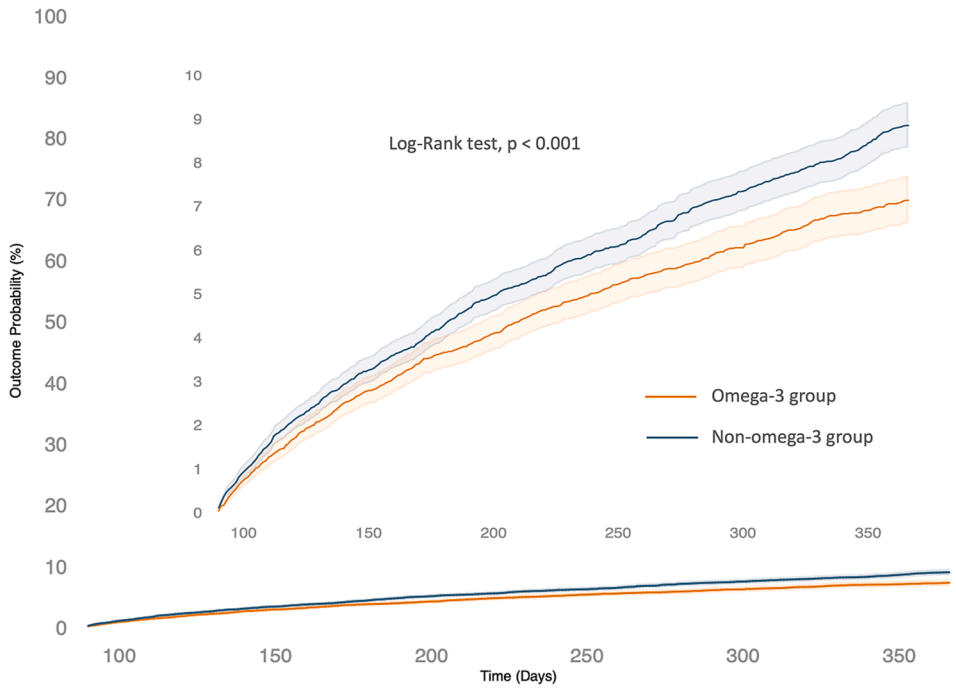

Fig. 2. The probability of the primary outcome—a composite of any psychiatric sequelae of COVID-19.

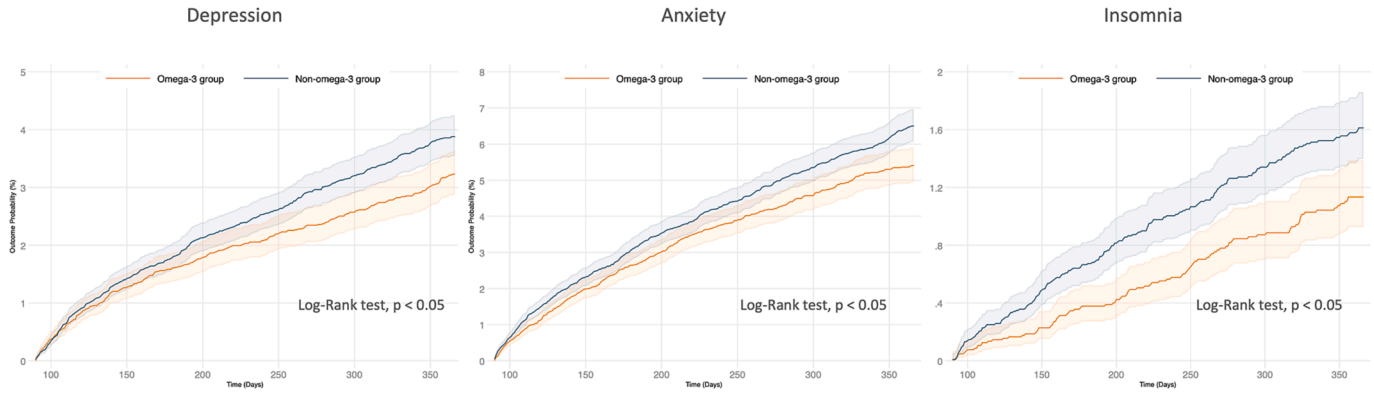

Fig. 3. The probability of each psychiatric sequelae of COVID-19.

associated with inflammation (Su et al., 2014). Regarding anxiety, a meta-analysis by Su et al., which integrated 19 clinical trials involving 2240 participants from 11 countries, demonstrated a correlation between improvement in anxiety symptoms and omega-3 PUFAs treatment in comparison to control groups (Su et al., 2018). This anxiolytic effect of omega-3 PUFAs was notably more significant in subgroups receiving a higher dosage (at least 2000 mg/day). In terms of sleep quality, several studies have suggested a positive impact of omega-3 on mitigating insomnia and enhancing sleep quality (Dai and Liu, 2020; Liu et al., 2017; Patan et al., 2021). For instance, a randomized controlled trial conducted by Patan et al. observed that healthy adults taking omega-3 PUFAs supplements (comprising 900 mg DHA/day and 270 mg EPA/day) experienced a significant increase in sleep efficiency and a considerable reduction in sleep latency compared to placebo groups (Patan et al., 2021). In line with these findings, our study discerned similar patterns wherein patients taking omega-3 PUFAs supplements prior to SARS-CoV-2 infection manifested a lower risk of developing subsequent depression, anxiety, and insomnia.

Our study adds to previous research on the beneficial impact of omega-3 on COVID-19 outcomes. Asher et al. found that patients with an omega-3 index over 5.7% had a 75% lower risk of mortality from COVID-19 (Asher et al., 2021). Another study demonstrated that critically ill COVID-19 patients who supplemented with EPA and DHA (at daily doses of 400 mg and 200 mg, respectively) had significantly improved one-month survival rates (21% versus 3%) compared to the control group (Doaei et al., 2021). Our investigation extends this exploration into the post-acute phase of the disease and focuses specifically on the preventive effects of omega-3 PUFAs supplementation. This adds depth to our understanding of the potential role of omega-3 PUFAs in managing COVID-19, particularly in patients with milder symptoms who did not require initial hospitalization or anti-viral agents.

The psychiatric effects post SARS-CoV-2 may be reduced by omega-3 PUFAs due to their beneficial effects on immunity, inflammation, and oxidative stress (Yang et al., 2022). They can potentially neutralize the virus's S protein, reducing ACE2-mediated viral infections, and preventing psychiatric sequelae (Alomari et al., 2020; Azargoonjahromi, 2022; Brann et al., 2020; Butowt and Bilinska, 2020). Omega-3 PUFAs can also counteract COVID-19 induced coagulopathy due to their antithrombotic effects, reducing cerebrovascular complications and subsequent psychiatric issues (Kazemi et al., 2021; Sojka et al., 2022). Lastly, omega-3 PUFAs can mitigate the virus-induced exaggerated inflammatory response, preventing neuronal damage (Calder, 2013;

Table 3
The hazard ratio and incidence for comparing matched Omega-3and Non-omega-3 group for the common symptoms of post-COVID-19 condition.

Outcome	Number of patients with outcome		Hazard ratio	(95 %CI)	P value
	Omega-3 group n = 16,954	Non-omega-3 group n = 16,954			
Chest/throat pain	222	267	1.126	(0.942, 1.345)	0.192
Abnormal breathing	202	246	1.110	(0.921, 1.337)	0.273
Abdominal symptoms	467	618	1.021	(0.905, 1.151)	0.734
Fatigue	206	296	0.937	(0.784, 1.119)	0.471
Headache	222	346	0.864	(0.730, 1.023)	0.090
Myalgia	40	89	0.606	(0.417, 0.880)	0.008
Loss of taste/ smell	10	10	0.450	(0.091, 2.231)	0.316
Cough	200	331	0.814	(0.683, 0.970)	0.021
Palpitation	55	92	0.807	(0.578, 1.127)	0.206
Cognitive symptoms	37	42	1.195	(0.768, 1.859)	0.429

Calder et al., 2020; Serhan, 2014; Zhou et al., 2022). Their anti-inflammatory properties and role in inflammation resolution may alleviate neuropsychiatric symptoms post-COVID-19. These mechanisms could explain the impact of omega-3′s on post-COVID-19 psychiatric sequelae.

Our study provides the first evidence of omega-3 PUFAs in preventing post-COVID-19 psychiatric sequelae. Despite potential biases such as misdiagnosis or documentation errors associated with registry databases, we leveraged a comprehensive, dynamically updated population-based database. This allowed us to explore a wide global population within contemporary timeframes. To minimize the risk of residual confounding, which propensity score matching can't entirely eliminate, we employed a rigorous methodological approach. Patients with pre-existing symptoms were excluded to ensure post-COVID-19 symptoms were correctly attributed. Groups were carefully matched in terms of baseline characteristics, socioeconomic determinants of health, and pre-existing medical comorbidities. We also excluded patients with T2DM, hypertension, and hyperlipidemia to mitigate potential omega-3 use for other therapeutic purposes. While propensity score matching was conducted, it's important to note that the pre-matching ratio of 1:6 between the two groups is primarily due to the initial disparity in the number of individuals using omega-3 within the database. Additionally, regarding secondary outcomes, despite the presence of certain inconsistencies in the impact of omega-3 supplementation across various population subgroups, it's worth noting that these discrepancies might stem from the reduced sample size within specific groups after grouping. Moreover, while we did not use BMI for covariates, we used ICD code E66 "Overweight and obesity" for propensity score matching. Despite the potential selection bias introduced by the lack of individual lifestyle data, efforts were made to mitigate this through socioeconomic matching. Additionally, we acknowledge that our study lacks data on queries by country and HCOs, inflammation level, measurement of omega-3 levels in the body, or the detailed methodology of omega-3 consumption measurement required for dose-specific analysis due to the limitation of TriNetX database. Future Prospective studies should focus on researching the optimal dosage and the relationship between the optimal dosage, the body's omega-3 levels, and inflammation index, while also addressing differences between countries.

5. Conclusion

In summary, our study reveals a link between omega-3 PUFA supplementation and a decreased risk of long-term psychiatric sequelae of depression, anxiety, and insomnia, following a SARS-CoV-2 infection. These findings suggest the need for further investigation through placebo-controlled clinical trials to assess the potential of omega-3 PUFAs as a preventive approach to mitigate adverse mental health outcomes in the post-acute phase of COVID-19.

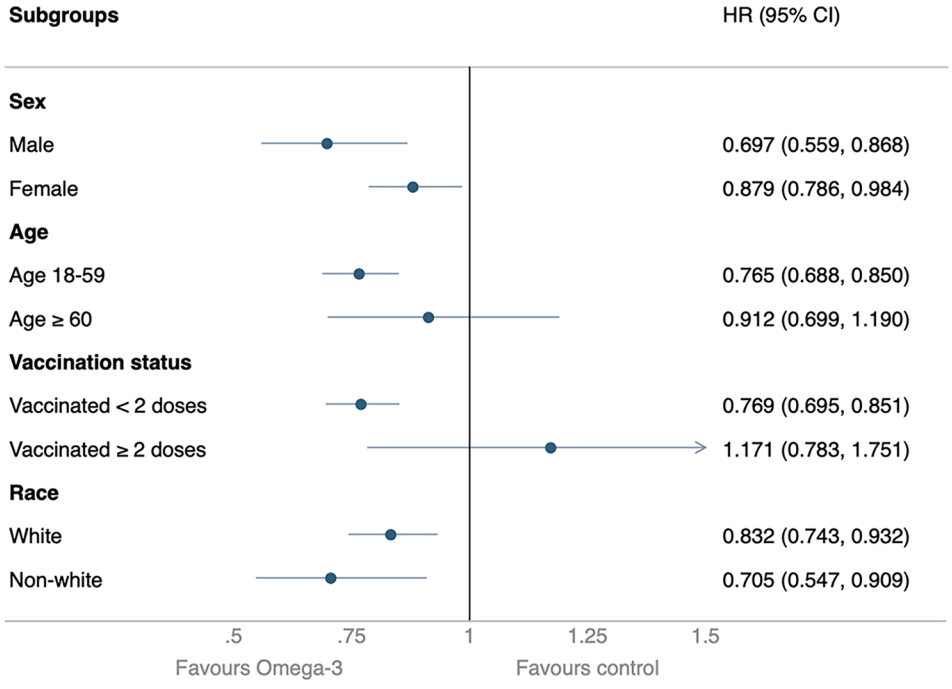

Fig. 4. Subgroup analyses of the risk of any psychiatric sequelae of COVID-19 between the omega-3and non-omega-3 group.

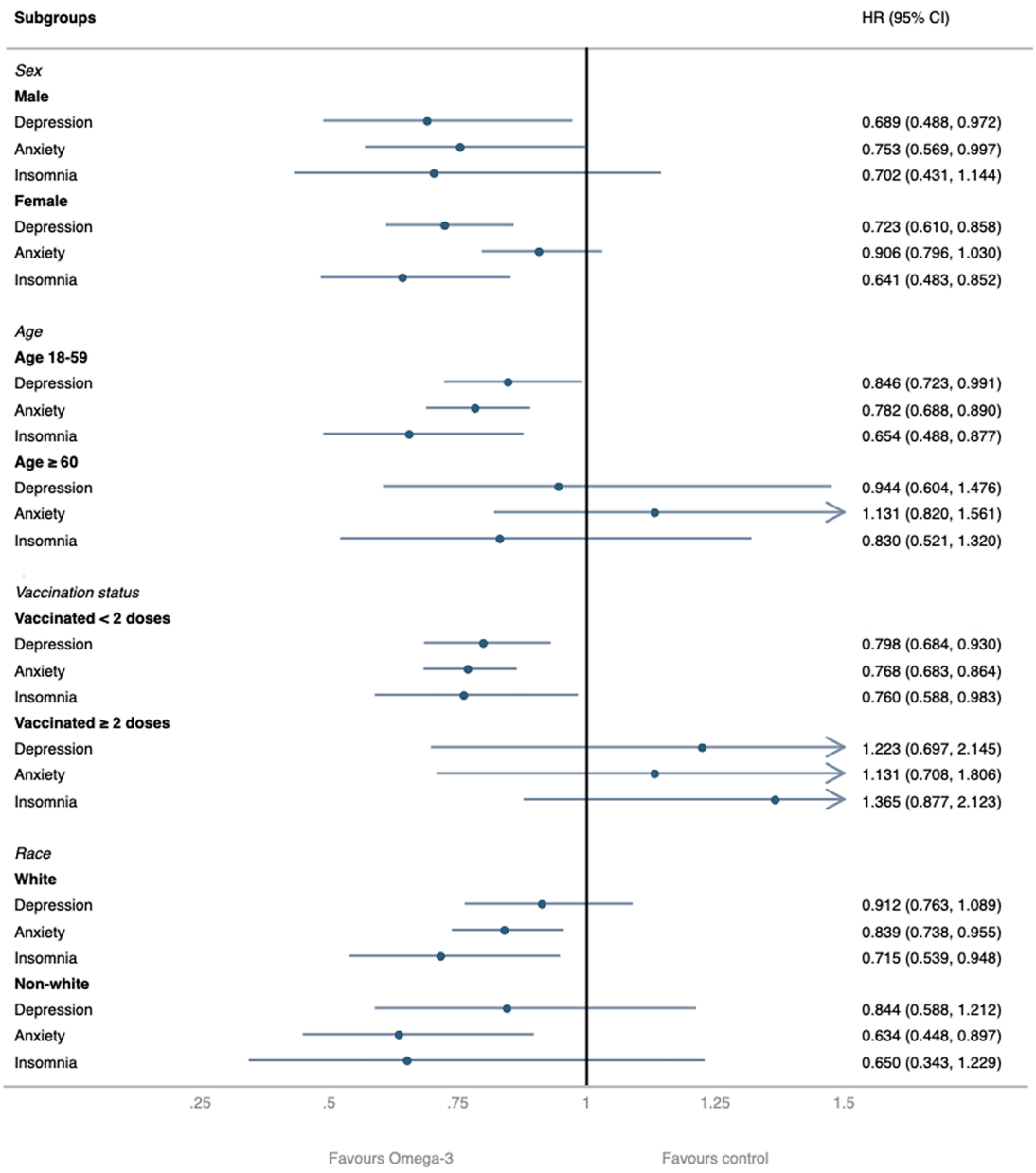

Fig. 5. Subgroup analyses of the risk of each psychiatric sequelae of COVID-19 between the omega-3and non-omega-3 group.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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