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Utilizing the omega-3 index to assess the relative bioimpact of a whole salmon oil and a concentrated omega-3 oil in healthy adults

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ABSTRACT

Background: Epidemiological studies indicate chronic global underconsumption of dietary omega-3 fatty acids with an increased risk of adverse health outcomes. Omega-3 supplements are frequently used to address this deficit. However, whole fish contains an array of other fatty acids with additional putative health benefits. The health outcomes of omega-3 supplementation trials have been highly variable, in contrast to trials assessing regular fish consumption.

Objective: Our goal was to evaluate the biological impact (bioimpact) of a whole salmon oil (OmeGo) compared to a commonly used, concentrated omega-3 oil. OmeGo is produced from fresh salmon using a patented protease hydrolysis process, leaving the salmon oil's natural food matrix intact. This could feasibly improve the oil's bioavailability and bioimpact.

Methods: In this randomized, active-controlled interventional study, 84 healthy subjects were randomized to receive OmeGo or an omega-3 supplement for 14 weeks to assess changes in red blood cell eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) quantified as the omega-3 index (O3I). Inflammatory biomarkers and sleep quality, two important determinants of well-being, were also assessed.

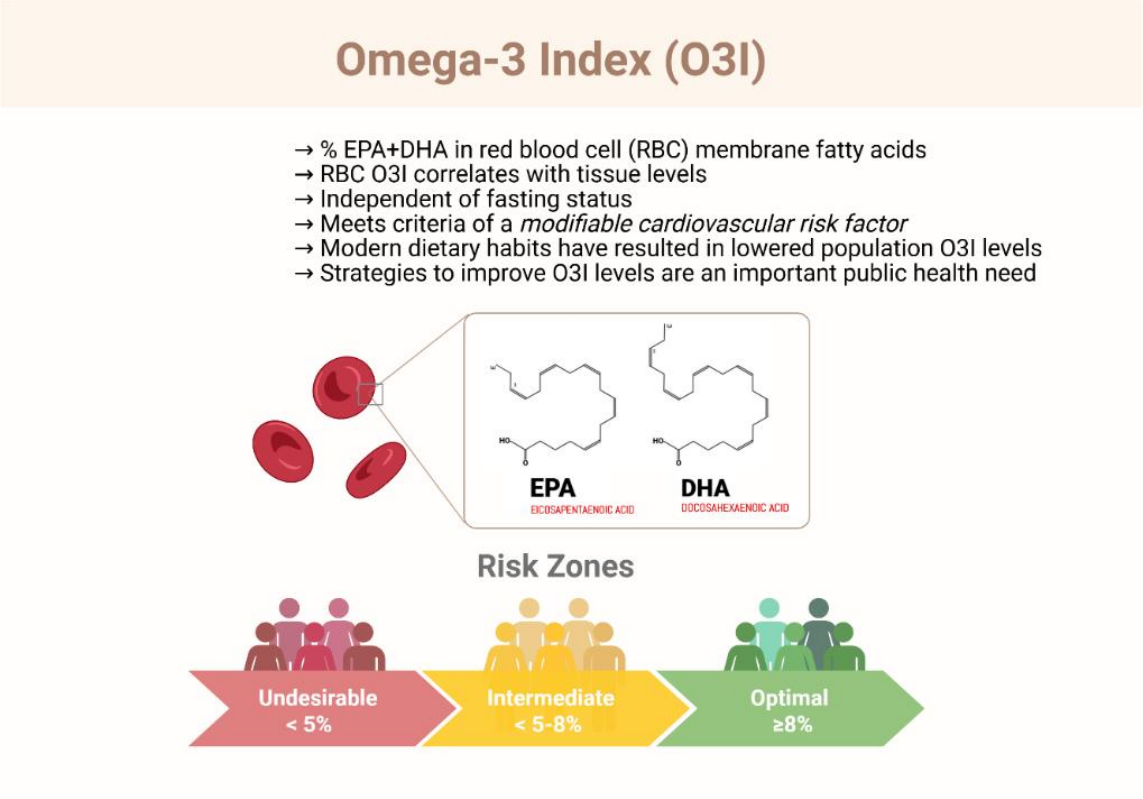
Results: Despite OmeGo containing 2.5-fold less EPA and DHA, the increase in O3I from baseline was 1.7-fold greater than the active comparator, corresponding to a 4.3-fold greater increase in O3I per 100mg of EPA+DHA ($p = 0.001$). High-sensitivity C-reactive protein (hsCRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) all decreased to a

greater extent in the OmeGo group, with between-group differences reaching statistical significance for hsCRP ($p < 0.01$) and TNF-α ($p < 0.05$).

Conclusion: The findings of this study indicate that a fish oil retaining its intact food matrix and natural omega-3 fatty acids levels is more bioavailable and better replicates the health benefits of regular fish consumption compared to a commonly used concentrated EPA/DHA supplement.

Novelty of Study: This study challenges the prevailing assumption that concentrated omega-3 supplementation is the most effective strategy for compensating for inconsistent fish consumption and attaining the health benefits associated with regular fish intake.

Keywords: omega-3 index; salmon oil, polyunsaturated fatty acids; eicosapentaenoic acid; docosahexaenoic acid; C-reactive protein; tumour necrosis factor-α; interleukin-6.



Graphical abstract: A summary of the definition and relevance of the omega-3 index (O3I) as a biomarker for health and disease risk. Figure created in https://biorender.com.

INTRODUCTION

Seafood played a central role in the diet of early modern humans, with marine food sources estimated to account for up to 50% of total dietary intake [1]. Marine foods, such as fish, are the primary source of the omega-3 fatty acids (O3 FAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which fish obtain from phytoplankton through the food chain. Among fish, oily varieties like salmon, sardines, and mackerel have significantly higher levels of these essential fatty acids

(EFAs) than their leaner counterparts. Once incorporated into tissues, EFAs function as bioactive compounds essential for maintaining normal human physiology. Additionally, marine fish oils provide functional polar lipids, fat-soluble vitamins, trace minerals, antioxidants, and carotenoids to support metabolic health and antioxidant defences [2-4].

Since humans lack the enzymes for de novo synthesis of O3 FAs, these essential nutrients must be obtained through the diet [5]. However, modern diets have shifted significantly, leading to a reduction in O3 FA intake resulting from changes in food processing and agricultural practices. Recent global estimates indicate that fewer than 20% of the world's population consume ≥250 mg/day of EPA and DHA, a level frequently considered as the lower limit of recommended daily intake associated with cardiovascular benefit [6]. Indeed, suboptimal diets, particularly those deficient in O3 FAs, are linked to a significant reduction in life expectancy, highlighting the need to address this imbalance through supplementation, the most common approach [7]. Marine aquaculture is also a vital means of providing fish nutrition and novel functional ingredients to an ever-expanding global population [8].

The scientific exploration of O3 FAs in human health began in the 1970s when Danish researchers observed that the Inuit population in Greenland had a notably low incidence of cardiovascular and metabolic disease and consumed a diet rich in marine fats [9]. Subsequent investigations suggested that higher circulating levels of O3 FAs in Inuit populations were linked to the reduced cardiovascular disease (CVD) risk [10-11]. This discovery triggered broader research into the health benefits of O3 FAs and led to the development of omega-3 supplements and the use of the omega-3 index (O3I) as a measure and biomarker of overall EPA+DHA status. However, this strategy assumes that the O3I has the same predictive power whether it is attained from eating fatty fish or an omega-3 concentrate. The latter goes through significant processing, including bleaching, deodorization, distillation, and reconstitution into either an ethyl ester or a triglyceride; therefore, it may not provide health benefits comparable to eating fresh fish.

Substantial epidemiological evidence, supported by meta-analyses, underscores the causal connection between consuming fatty fish and a reduced risk of CVD and mortality [12-16]. However, whilst some earlier trials have shown a benefit with O3 FA supplementation for CV-event risk reduction, results from contemporary studies have been inconsistent [17-20]. A comprehensive review analysing data from 86 randomized controlled trials (RCTs) concluded that the evidence supporting cardiovascular benefits from omega-3 supplementation was inconclusive, demonstrating only a marginal reduction in coronary heart disease (CHD) mortality risk [21]. The 13,000-patient STRENGTH study, which included a prespecified analysis by achieved O3 levels, did not demonstrate a cardiovascular benefit with omega-3 supplementation (4g/day) compared to placebo. Moreover, participants achieving higher omega-3 blood levels also did not exhibit a reduction in cardiovascular events either [22]. Together, this raises the question of whether omega-3 supplementation can be assumed to provide the same underlying health benefits as regular fish consumption despite raising the O3I.

OmeGo is a minimally processed salmon oil produced by enzymatic hydrolysis of the side streams of freshly filleted salmon. The protease enzymes have no lipase activity and therefore have no impact on the oil fraction. OmeGo provides a full spectrum of omega fatty acids in natural ratios, within a food matrix that may enhance bioactivity, offering a nutritional profile akin to that of fresh fish. Along with omega fatty acids, it contains other bioactive ingredients like carotenoids (astaxanthin), specialised pro-resolving mediators of inflammation (SPMs), and lipopeptides. Prior research has shown that OmeGo significantly modulates both type I and type II (allergic) inflammation [23-24]. This broad inflammation-

resolving profile is reflected clinically with OmeGo supporting an improved immune response and recovery from viral infection as well as improved sleep quality and respiratory symptoms in individuals troubled by particulate matter pollution [25-26]. Further, OmeGo achieved a 3- to 5-fold greater reduction in oxLDL in healthy adults than algae oil and a concentrated omega-3 oil despite these oils containing significantly higher levels of O3 FAs [27].

This 14-week clinical trial investigated the effects of OmeGo supplementation compared to a popular omega-3 supplement (Seven Seas; SSO3) on changes in the O3I, inflammatory biomarkers, and sleep quality. The trial hypothesis was two-fold. Firstly, as OmeGo is a natural food matrix, it may have significantly better bioavailability, enabling at least an equivalent increase in O3I despite the daily dose of the SSO3 oil containing 2.5 times more EPA and DHA. Secondly, to replicate the inflammation-resolving effects of fatty fish nutrition, a broad array of fatty acids contained in whole fish would be needed rather than a concentrated level of EPA and DHA. Ultimately, this trial would help determine whether a whole fish oil supplement more faithfully replicates the health benefits associated with consuming whole fatty fish and challenge the entrenched orthodoxy that consuming processed concentrated omega-3 supplements is the superior strategy for supporting health.

MATERIALS AND METHODS

This study was conducted as a decentralised trial supported by the Alethios research software platform. This enables the remote and digitised collection of clinical data and therefore does not require formal research sites, thereby broadening the reach for participant recruitment. Participant recruitment via social media advertisements, electronic data collection (via smartphones/laptops and wearable devices), and study monitoring, and the distribution of at-home testing kits were managed by the Alethios platform. The study adhered to Good Clinical Practice (GCP) Guidelines and was conducted in accordance with ethical principles originating from the Declaration of Helsinki, consistent with ICH/GCP and applicable regulatory requirements. The study protocol, the participant information, and the informed consent form were submitted to and approved by the regional institutional review board (IRB), Sterling IRB (approval number 12784-CCurrie, protocol number HBC-CARDIO-2024-001-v2) before initiating participant enrolment. The study was registered on clinicaltrials.gov, NCT06802068.

Inclusion and exclusion criteria: Eligible participants were healthy adults aged between 40 and 80 years. Participants were required to have a stable body weight (± 5kg / 11lbs) for the prior 3 months and be capable of giving informed consent. Participants were also required to own a wearable device from one of the pre-specified device families of Apple, Fitbit, Garmin, Google Fit, or Oura Ring. Any current use of omega-3 supplementation, fish or seafood allergies, pregnancy, as well as any gastrointestinal malabsorption states or being an active smoker were key exclusion criteria.

Interventions: Alethios used block randomization to assign participants to 2 capsules of OmeGo daily (containing 100mg EPA+DHA) or 1 capsule of Seven Seas omega-3 oil (containing 250mg of EPA+DHA), both administered as per labeled instructions. Compliance was supported by daily reminder messages from the Alethios platform and checked at the end of the study via a capsule count. Supplementation was provided for 14 weeks, followed by a 4-week follow-up period to assess persistence of effect at week 18. Research evidence indicates that minimal change in O3I is expected during the first 6 weeks and that at least 12-14 weeks of supplementation would be needed to see a change of at least 0.5% in the O3I [28-29].

OmeGo is a whole salmon oil liberated by enzymatic hydrolysis of fresh Norwegian Atlantic salmon (*Salmo salar*), manufactured according to Good Manufacturing Practices (GMP) for food facilities, and complies with the Hazard Analysis and Critical Control Points (HACCP) principles. The fatty acid composition reflects that of salmon, with around 16% omega-3 (including EPA, DHA, DPA, and ALA), limited amounts of omega-5, 16% omega-6, 2.8% omega-7, 43% omega-9, and 2.6% omega-11. In terms of EPA and DHA (the focus of the O3I), OmeGo contains 50mg per 1000mg, and hence two capsules provided 100mg of EPA and DHA per day. The oil also contains minor fatty acid fractions, lipopeptides, and astaxanthin, which naturally stabilize the oil, giving it a 4-year shelf life. The product has US FDA New Dietary Ingredient status (NDI) and is produced by Hofseth Biocare ASA (Ålesund, Norway) and encapsulated by Pharmatech AS (Rolvsøy, Norway).

Seven Seas omega-3 (SSO3) is a popular omega-3 supplement and is a cod-liver oil extracted from British cod fish. Each capsule provides 250 mg of EPA and DHA, corresponding to the manufacturer's recommended daily dose. Accordingly, participants randomized to the 2.5-fold group had a higher daily intake of EPA+DHA than those in the OmeGo group.

Randomization: Participants were allocated to study groups by block randomization after completing the electronic informed consent (eConsent). Randomization was implemented by the Alethios platform and was monitored by the designated study statistician.

The study targeted a recruitment of 48 participants per group for a total of 96 participants. Assuming an average increase in bioavailability, defined as a rise in the O3I of 0.5 percentage points within the comparator group, the necessary sample size to detect a mean difference of 0.2 percentage points was calculated to be 37 individuals in each group, totaling 74 subjects. This calculation was based on an assumed bioavailability standard deviation of 0.3 in both groups, a significance level of 5%, and a power of 80%. With a 10% attrition rate, the number of participants needed was 82. To account for uncertainty in the SD estimate, the final enrollment target was set to 96 participants.

Endpoints and assessments: The primary endpoint was the change in omega-3 index (O3I) at 14 weeks and at week 18 following a 4-week washout period to assess for persistence of effect. O3I represents the combined percentage of EPA and DHA in red blood cell (RBC) membrane fatty acids as a percentage of eleven fatty acids present in the RBC membrane. The RBC is typically used as it is easily accessible and reflects important health metrics, including cardiovascular health risk and brain structure [30-31].

A dose-corrected analysis was also prespecified as a secondary analysis to assess the change in O3I per 100mg of EPA and DHA. The other secondary analyses assessed changes in the inflammatory biomarkers hsCRP, TNF-α, and IL-6; objective sleep quality and heart rate variability (HRV) with subjective sleep assessment as an exploratory endpoint.

Sample collection, preparation, and storage: O31 analysis was conducted using dried blood spot (DBS) samples, a validated method for assessing EPA and DHA levels in blood. Capillary blood was collected at home using standardized DBS kits.

In brief, blood was obtained via a finger-prick using a sterile, single-use lancet, and approximately 1–2 drops of capillary blood were applied onto pre-printed circles on antioxidant-treated filter paper cards.

Three DBS samples were collected at baseline, day 98 (week 14), and day 126 (week 18) on antioxidant-stabilized paper to minimize oxidative degradation of EPA and DHA during drying, transport, and storage. Following application, samples were allowed to dry at ambient temperature before being sealed in airtight, light-protected bags containing desiccant.

Following drying, DBS cards were stored and shipped under standard conditions without refrigeration. Validation work has demonstrated that EPA+DHA levels in DBS samples remain stable for extended periods when collected on antioxidant-treated paper. This stability enables cost-effective shipment using routine postal services rather than requiring cold-chain transport, making DBS highly suitable for decentralized studies. Further, DBS shows higher accuracy than the gold standard of venous whole blood sampling for the inflammatory biomarkers hsCRP, TNFα, and IL-6 [32].

Fatty acid analysis and O3I calculation: DBS samples were processed according to established fatty-acid extraction and gas chromatographic procedures [33]. A standardized 6 mm punch was taken from each blood spot to ensure consistent sample volume. Fatty acids were extracted from the DBS matrix and converted to fatty acid methyl esters (FAMEs) via acid-catalyzed transesterification. FAMEs were subsequently analyzed by gas chromatography using flame-ionization detection (GC-FID) to quantify the individual fatty acids as a percentage of total identified fatty acids.

This approach has been validated across diverse sample sets and has demonstrated high reproducibility and precision for EPA and DHA measurements. For example, DBS EPA+DHA content correlates strongly ($r \approx 0.97$) with EPA+DHA measured directly in erythrocytes, confirming its suitability as a surrogate for calculating the O3I [33].

Because DBS samples contain whole blood rather than isolated erythrocytes, a conversion equation is applied to translate DBS EPA+DHA values to the corresponding erythrocyte-derived O3I. This conversion has been previously validated in human studies, enabling the accurate estimation of the O3I from DBS samples.

Pro-Inflammatory Biomarkers: The other DBS panels were used to assess the systemic pro-inflammatory markers hsCRP, TNFα, and IL-6.

Biomarker extraction was carried out using standardized 6mm punches from each blood spot, placed in extraction phosphate-buffered saline containing 0.05% Tween-20, and a protease inhibitor buffer for overnight elution at 4°C with gentle agitation. The extraction volume was optimized to achieve concentrations within the linear range of each assay while accounting for the estimated blood volume per punch (approximately 7-8 µL).

The inflammatory biomarkers were quantified using commercially available high-sensitivity ELISA kits validated for use with DBS elutes. Standard curves were prepared using manufacturer-provided recombinant proteins, and DBS elute concentrations were calculated using established conversion factors to account for dilution during extraction and the hematocrit effect. Quality control samples at low, medium, and high concentrations were included in each analytical batch to ensure precision and accuracy. Intra-assay and inter-assay coefficients of variation were maintained below 10% and 15%, respectively. The lower limits of quantification for hsCRP, IL-6, and TNFα were 0.1 mg/L, 0.5 pg/ml, and 0.5 pg/ml, respectively, with upper limits sufficient to capture the expected physiological ranges in adults. All biomarker concentrations were expressed as whole-blood equivalents, rather than normalized or standardized serum values.

Sleep and activity levels: Wearable devices were used to assess activity levels (step count), stress-related autonomic function (heart rate variability [HRV]), and sleep quality (number of nocturnal awakenings).

Subjective sleep quality was an exploratory endpoint. This was assessed using the Basic Nordic Sleep Questionnaire (BNSQ), a validated, standardized, frequency-anchored instrument (1–5 scale per item with a higher score reflecting poorer sleep) covering insomnia symptoms, sleep maintenance, subjective sleep quality, and daytime consequences (i.e., tiredness and napping) [34].

Statistical analysis: Standard descriptive statistics are used to summarize demographic and baseline information across the study groups, including mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. Outcomes were plotted with means and corresponding 95% confidence intervals for each group, and statistical significance was analyzed by estimating mixed models with study group and categorical time (days 98 and 126) and interaction terms as model covariates and adjusting for baseline measurements. The longitudinal structure of the data was handled by allowing for random intercepts across participants. Wake-up events were measured daily, and natural cubic splines were used to model trajectories over time in both groups, with spline terms in the mixed model analysis. Differences between groups were assessed using Wald tests to test whether the interaction terms were all equal. The significance level was set at 5% throughout, and all analyses were done using Stata version 18.0.

RESULTS

Baseline demographics and supplement tolerability: A total of 96 participants were randomized, and 84 participants completed the 14-week supplementation period and returned the DBS tests. Nine participants withdrew from the study; the common reason was an inability to connect their wearable device to the research platform (n=5). The other reasons were split equally between an inability to undertake a DBS capillary blood test at baseline, being a vegetarian (and not wanting to consume a fish-derived supplement), difficulty in swallowing the capsules, and no longer wanting to participate in the study. Five of the subjects who withdrew were in the OmeGo group, and four were in the SSO3 group (see Figure 1). Adherence to supplementation was high in both groups: 97% with OmeGo and 95% with SSO3.

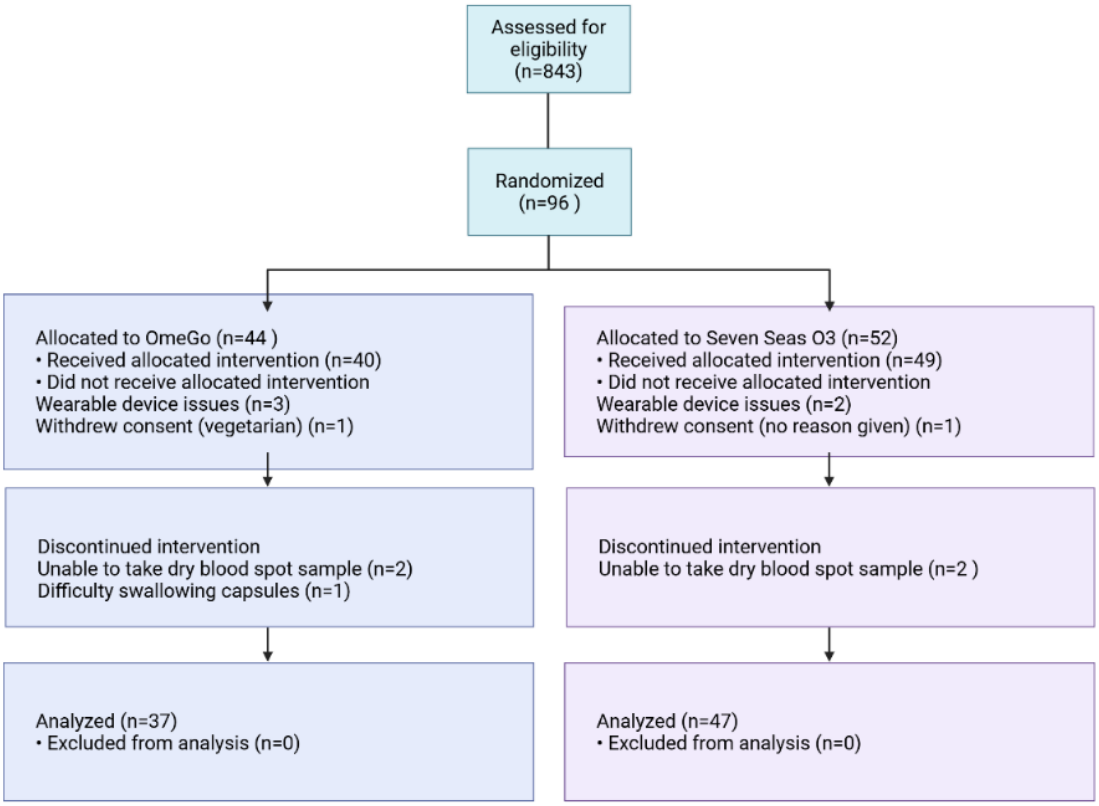


Figure 1. Enrollment, randomization, follow-up, and analysis of participants. Figure created in https://biorender.com.

Baseline demographic characteristics were generally well balanced between the two arms, especially for those that impact O3I response to supplementation (see Table 1). The baseline O3I was 5.25% in both groups, and the average age was 53.7 years and 52.1 years, respectively. Regarding sex, the majority of participants were female, accounting for 68% of participants in the OmeGo group and 77% in the SSO3 group. Mean BMI at baseline was 26.0kg/m² (range 21.0 kg/m²-32.5 kg/m²) in the OmeGo group and 25.9kg/m² (range 21.1 kg/m²-32.5 kg/m²) in the SSO3 group. Wearable devices were also well balanced across the groups, and 80% were either a Fitbit or an Apple Watch. The balance was made up by Garmin (8%), Google Fit (8%), and Oura Ring (4%). For ethnicity classification, anyone reporting more than one ethnicity was registered as "Mixed" and anyone identifying their ethnicity as "other" and with no more than one ethnicity was registered as "Other".

Table 1. Key baseline demographics of participants randomised to OmeGO salmon oil

	OmeGo2g/d	n	Seven Seas 1g/d	n
Age, mean (SD)	53.7 (7.6)	37	52.1 (10.7)	47
Female	68%	25	77%	36
Male	32%	12	23%	11
Ethnicity				
African-American	3%	1	8.5%	4
Asian	16%	6	11%	5
Caucasian	67.6%	25	66%	31
Latino or Hispanic	0%	0	4%	2
Mixed	8%	3	8.5%	4
Other	5.4%	2	2%	1
O3I	5.25%		5.25%	
BMI	26		25.9	

This table summarises key baseline demographics of participants randomised to OmeGo salmon oil (n=37) & Seven Seas oil (n=47) and who completed all assessments, including DBS testing.

Overall change in Omega-3 index (O3I) during supplementation period: The O3I analysis was performed on the 84 subjects who took the allocated supplement and returned their respective DBS tests. From the same baseline O3I level, both groups showed a significant and progressive increase in O3I over the course of the study (see Figure 2). At the end of the supplementation period, on day 98, there was a 6% increase in the comparator group mean O3I corresponding to an increase from 5.25% to 5.55% ($p<0.001$). From day 98 to day 126, there was a further small but significant increase in O3I ($p<0.05$) to 5.62% equating to a 7% increase from baseline (Figure 2). OmeGo also showed a significant increase from baseline in O3I of 10% at day 98, with an O3I of 5.76% ($p<0.001$). This represents a 73% greater change in O3I with OmeGo compared to SSO3. The change in O3I also continued to increase in the OmeGo arm, reaching 12% above the baseline (O3I = 5.88%) at day 126 ($p<0.001$).

Comparing across groups, the change in O3I driven by OmeGo was significantly greater than that by the SSO3 oil at both day 98 ($p<0.001$) and day 126 ($p<0.001$).

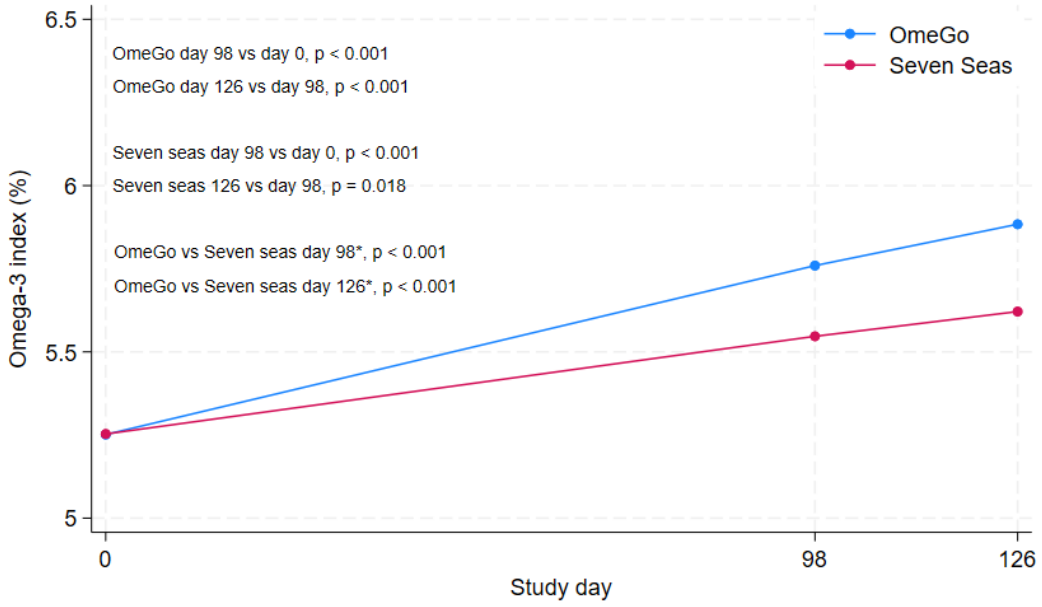


Figure 2. Change in omega-3 index (O3I) measured as a percentage of the red cell membrane fatty acids at baseline, day 98 (week 14), and day 126 (week 18).

Change in O3I from end of supplementation period to end of study: As noted above, the O3I increased in both arms from day 98 (end of supplementation) to day 126 (end of study), indicating that a significant proportion of participants continued taking the supplements up to week 18. Indeed, the end-of-study capsule count indicates that around two-thirds of participants continued supplementation. Consistent with this, around 15% of participants in both groups were identified as showing a decline in O3I from day 98 to day 126, with a further 15%-20% showing a plateauing in O3I level. A secondary analysis of the subgroup who showed either plateauing or decline in O3I after day 98 showed a mean decline of 1% in O3I, suggesting a good persistence of effect. However, with limited numbers in this group, the generalizability of this data is limited. Unsurprisingly, in those who continued supplementation, O3I continued to rise at a similar rate as during the first 98 days.

Change in O3I per 100g of EPA and DHA: The dose-adjusted change in O3I was assessed to determine the change in O3I per 100mg of EPA and DHA, the omega-3 fatty acids (PUFAs) used to assess the O3I. In the primary analysis above, the 1.73-fold greater change in O3I was observed in the OmeGo arm compared to the Seven Seas arm with EPA and DHA doses of 100mg and 250mg, respectively. With a dose-correction to scale to equivalent EPA and DHA doses, OmeGo demonstrated an apparent 4.3-fold greater bioavailability in terms of the incorporation of these fatty acids into RBC membranes and therefore, greater availability for downstream health benefits, as assessed by changes in inflammatory blood biomarkers.

Change in inflammatory biomarkers: DBS samples collected at baseline, day 98, and day 126 to assess hsCRP, TNF-α, and IL-6 (see Table 2), showed progressive declines in these inflammatory markers over the course of the study in both groups (see Table 2 and Figures 2-4). It should be noted that the results are based on normal immediate serum tests and that DBS values may differ and need to be normalised for a valid comparison to established normal ranges.

Table 2. Pro-inflammatory biomarker analysis from DBSs taken at baseline, day 98 (end of supplementation period), and day 126 (end of study).

Inflammatory marker		Baseline	Day 96	OmeGo v SS	Day 126	OmeGo v SS
hsCRP (mg/L)	OmeGo	3.22	2.79 (-13.2%)	p <0.001	2.69 (-16.5%)	p =0.01
	Seven Seas (SS)	2.92	2.66 (-8.9%)		2.6 (-10.9%)	
TNF (pg/ml)	OmeGo	18.7	16.3 (-12.1%)	p <0.001	15.1 (-19.1%)	p =0.002
	Seven Seas (SS)	24.9	23.3 (-6.4%)		22.1 (-11.1%)	
IL-6 (pg/ml)	OmeGo	24.9	23.1 (-7.3%)	p <0.01	22.3 (-10.8%)	p =ns
	Seven Seas (SS)	26.8	25.9 (-3.5%)		25 (-6.7%)	

High sensitivity C-reactive protein (hsCRP): For hsCRP, at day 98 in the Seven Seas group, there was a relative mean decrease of -8.9% (p<0.001 vs baseline) and -10.9% by day 126 (p=0.1, day 126 vs day 98). The OmeGo group showed a mean decrease of -13.2% and -16.5% in hsCRP at day 98 (p<0.001 vs baseline) and day 126, respectively (p=0.01 vs day 98). The mean declines in hsCRP were significantly greater in the OmeGo group compared to the SSO3 group at the end of the supplementation period (day 98, p<0.01) and at the end of the study (day 126, p=0.001) (see Figure 3).

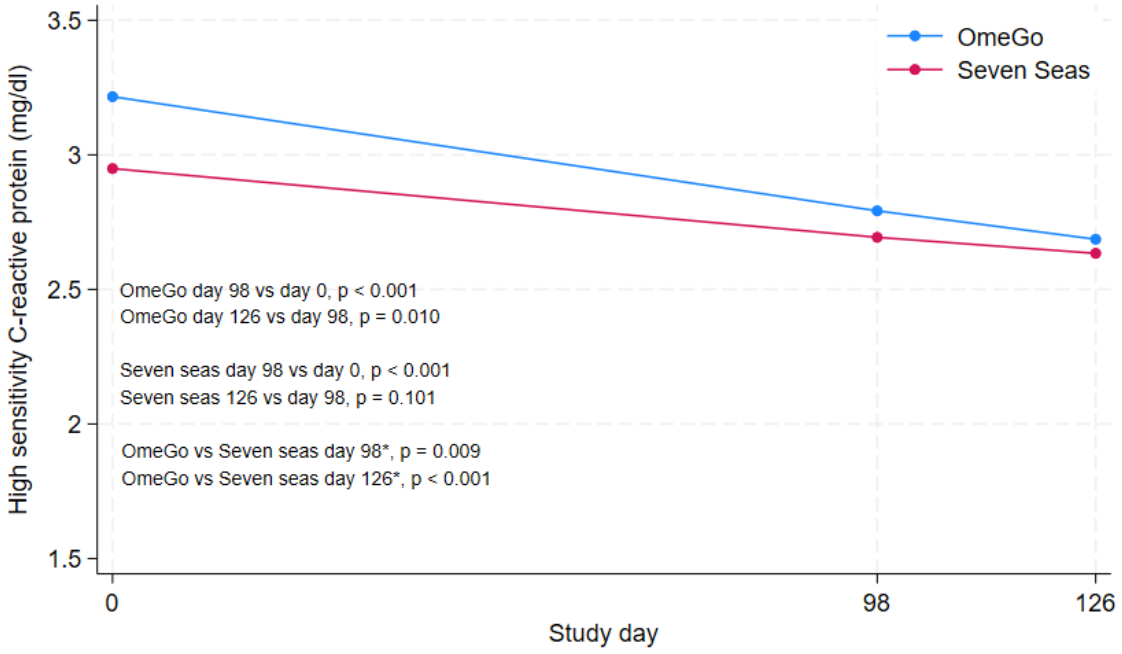


Figure 3. Change in hsCRP levels (mg/dl) in DBS samples measured at baseline, day 98, and day 126.

Tumour Necrosis Factor alpha (TNF-α): The change in TNF-α showed a similar pattern to hsCRP. In the SSO3 group, the mean reductions from baseline to day 98 were 6.6% (p=0.002) and from day 98 to day 126 were 11.2% (p=0.24) (see Figure 4). In the OmeGo, the mean reductions in TNF-α levels were 12% (p<0.001 vs baseline) and 19% (p=0.01 vs day 98), respectively. The mean declines in TNF-α were again significantly greater in the OmeGo group compared to the SSO3 group at the end of the supplementation period (day 98, p=0.044) and at the end of the study (day 126, p=0.008).

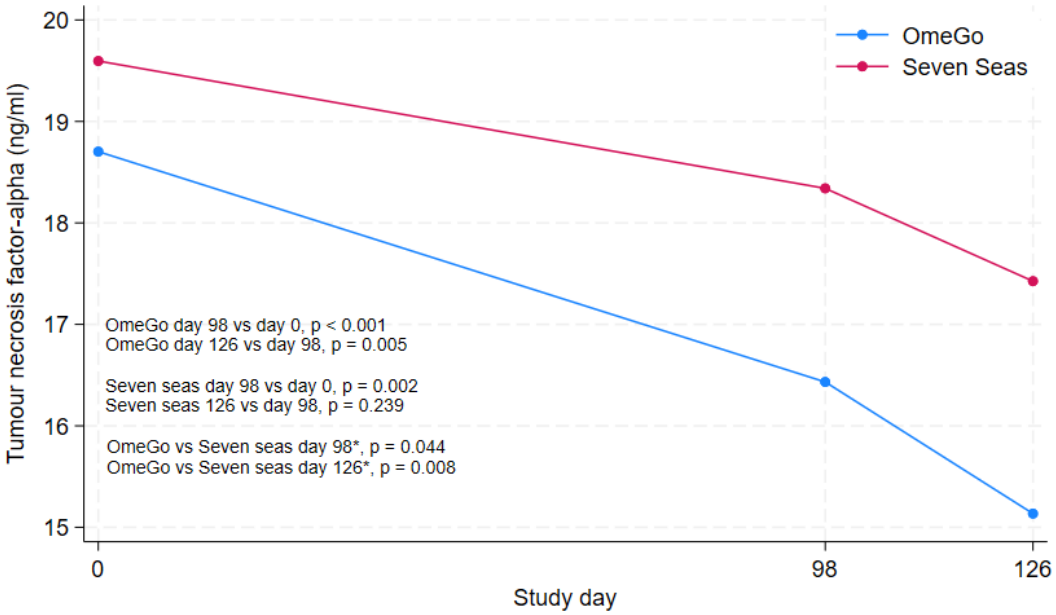


Figure 4. Change in TNF-α levels (ng/ml) in dry blood spot samples measured baseline, day 98 and day 126.

Interleukin-6 (IL-6): The mean changes in IL-6 were numerically greater in the OmeGo group than in the SSO3 group, although the between-group difference did not reach significance at either time point. In the SSO3 group, compared to baseline, there were non-significant decreases in IL-6 of 3.5% at day 98 (p=0.09 vs baseline) and 6.7% at day 126 (p=0.1vs day 98). In the OmeGo group, the mean decline in IL-6 of 7.3% at day 98 was significant (p=0.004). At day 126, the overall decline of 10.6% was not significant compared to day 98 (p=0.18) (see Figure 5).

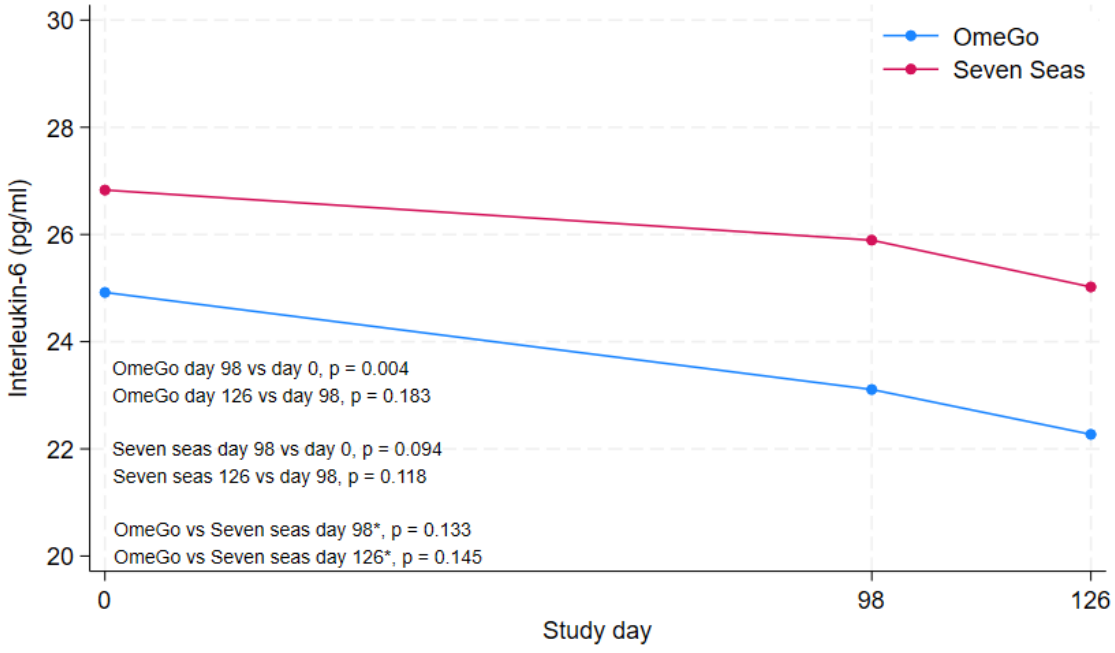


Figure 5. Change in IL-6 levels (pg/ml) in DBS measured at baseline, day 98, and day 126.

Objective sleep quality - number of awakening events per night: Sleep quality was assessed by the number of awakening events measured by the eligible wearable devices. At baseline, the OmeGo group had a mean rate of wake-up events almost two-thirds higher than the SSO3 group, which then declined by about 20% by end of the study (day 98). In contrast, there was a progressive increase in wake-up events of around 20% in the SSO3 group by study end the mean number of wake-up events was similar in the two groups (see Figure 6). No statistically significant difference was seen between the arms (p=0.37). From day 98 to day 126, the number of wake-up events showed minimal change

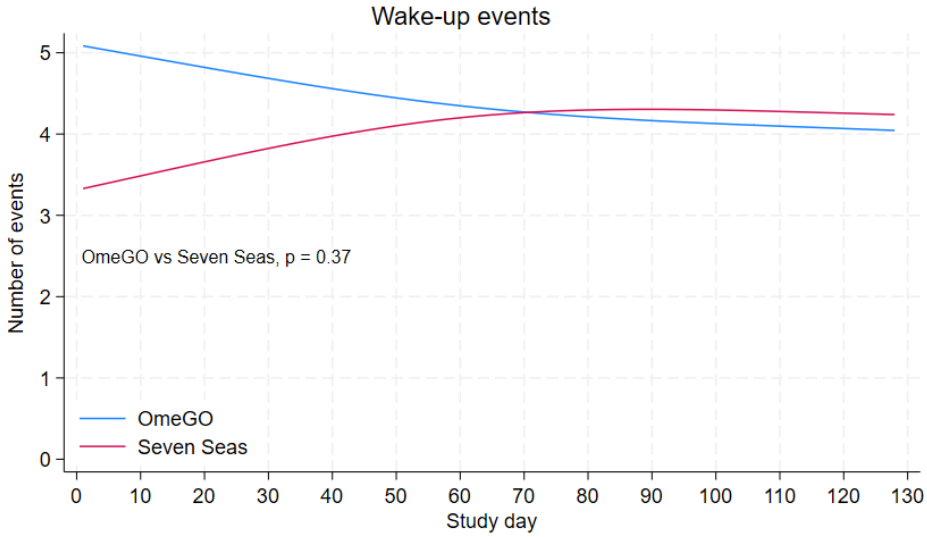


Figure 6. Trend analysis measuring the change in wake-up events over time measured by wearable device.

Subjective sleep quality - Basic Nordic Sleep Questionnaire: As an exploratory endpoint, the Basic Nordic Sleep Questionnaire (BNSQ) was used to assess whether participants reported any improvements in sleep quality. From baseline to the end of the study (day 98), the overall mean score declined significantly by -0.2 from baseline in the OmeGo arm and by -0.4 in the SSO3 arm at day 98 (see Figure 7). By day 126, there remained a small change from baseline.

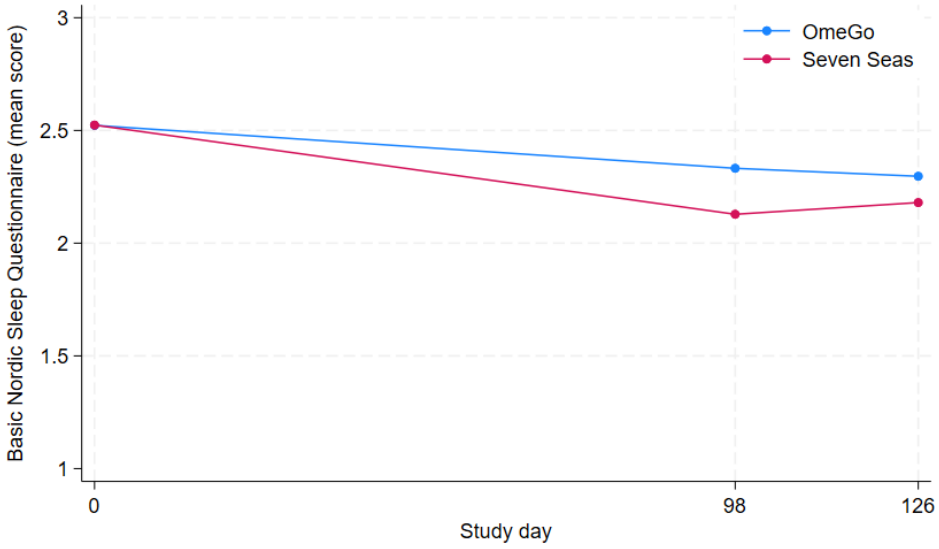


Figure 7. The change in the Basic Nordic Sleep Questionnaire (BNSQ) measured at baseline, day 98, and day 126.

DISCUSSION

The chronic underconsumption of fish, reflected in sub-optimal population O3I levels, is well recognised to have a negative impact on health and longevity. Omega-3 supplementation has therefore become a widely adopted means to attempt to address this deficit. However, emphasis has predominantly been placed on the EPA and DHA content of supplements rather than on their bioavailability and downstream health benefits.

This decentralised, randomised, active-controlled, blinded clinical trial explored the impact of two different supplementation strategies on the O3I, systemic inflammation, and sleep quality. By comparing a whole salmon oil supplement (OmeGo), which contains the full spectrum of fatty acids present in fish within a natural food matrix, and a commercially available concentrated omega-3 oil (Seven Seas/SSO3) the study enabled the assessment of both the contribution of EPA and DHA dose and the influence of industrial processing of fish oil on O3I and anti-inflammatory clinical outcomes.

84 healthy participants received either OmeGo or the SSO3 comparator for 14 weeks (98 days). This was followed by a 4-week post-intervention period to assess persistence of effect. Both oils were dosed according to label instructions, providing daily intakes of 100mg EPA and DHA with OmeGo and 250mg with SSO3. Both oils contain triglycerides (TGs), which have superior bioavailability compared to oils composed of ethyl ester (EE) formulations [35].

Despite the 2.5-fold higher EPA and DHA content in the active comparator omega-3 oil, the between-group mean increase in O3I was significantly greater ($p<0.001$) in the OmeGo group at both day 98 (week 14) and day 128 (week 18).

At the primary endpoint (day 98), the absolute increase in O3I was 0.51% (+9.7% relative to baseline) with OmeGo and 0.29% (+5.6% relative to baseline) with the SSO3 comparator. By day 128, the mean absolute increase from baseline was 0.63% with OmeGo and 0.37% with the comparator. Thus, at both timepoints the increase in O3I with OmeGo was approximately 70% greater than that with the active comparator. After adjustment for EPA+DHA dose, a prespecified secondary analysis to assess relative bioimpact, the increase in O3I was over four-fold versus the comparator.

The O3I reflects the percentage of EPA and DHA incorporated into RBC membranes and therefore provides insight into the adequacy of dietary omega-3 intake. The uptake of O3 FAs and consequently the O3I are influenced by factors such as age, sex, and body mass index (BMI). In particular, a greater adiposity and a higher baseline O3I have been identified as key factors that can attenuate the O3I response [36-38]. Importantly, baseline demographics were well balanced between the groups and compliance with supplementation was high, at 97% with OmeGo and 95% with the omega-3 comparator group.

At baseline, mean O3I values were 5.25% in both groups. This corresponds to an intermediate O3I level: an O3I level of above 8% is considered cardioprotective, whereas levels below 4%-5% are strongly associated with an increased risk of cardiovascular disease, other chronic conditions and reduced life expectancy [29].

For context, healthy US adults in The Framingham Heart Study had a mean O3I of 5.3%, placing our study population broadly in line with that cohort [39]. However, several other studies have reported substantially lower O3I levels in US adults, including the much larger NHANES analysis, which found a mean O3I of 3.1% [40]. On this basis, the present study may have recruited a relatively healthier population with respect to O3I compared to the general US population. Such an outcome is consistent with the self-selection of health-conscious individuals motivated to participate in a dietary supplement-based clinical trial.

A review of the literature indicates considerable variability in the impact of diet or supplementation on O3I, with short-term studies frequently reporting

increases of 0.5% to 1.0% [41]. This variability likely reflects the influence of baseline O3I, age, sex, and BMI on the O3I response. As participants were not screened for baseline O3I, conservative assumptions were used in the study design. Accordingly, the study was powered to detect a minimum absolute increase in O3I of 0.5% and a between-group difference of 0.2%.

Supplementation was planned to stop after 98 days (14 weeks), in accordance with the protocol, to then assess persistence of effect out to day 126 (week 18). However, the end-of-study capsule count indicates that around two-thirds of participants had continued taking their allocated supplement. Unsurprisingly, therefore, a further increase in O3I, broadly in line with the previous O3I kinetics, was observed in both arms from day 98 to day 126. One-third of participants who discontinued supplementation on day 98 exhibited a plateau or small decline in O3I between weeks 14 and 18, typical of the slow wash-out kinetics of fatty acids from the body [42-43]. On such a day, results of 98 to 126 better reflect the impact of ongoing supplementation rather than an assessment of the persistence of effect.

The health benefits of O3 FAs, together with the other unsaturated fats found in fish, are well recognised. Yet the chronic underconsumption of these essential fatty acids remains a significant public health concern. Omega-3 supplementation has become a popular way to address this deficit, and the market comprises products derived from different fish species (typically anchovy, herring, and mackerel) in differing chemical forms, including TGs and EEs. These supplements offer higher concentrations of O3 FAs than those found in fish, achieved through extensive industrial processing. This typically includes degumming, bleaching, deodorisation, molecular distillation, re-esterification, and then the addition of vitamin E/tocopherols for stability [44]. This processing enables both a concentration of the omega-3 and the removal of oxidation products and environmental contaminants [45]. However, it also produces an oil that has undergone substantial processing, resulting in a composition that differs from the native oil, both in its fatty acids and food matrix. These changes may impact bioactivity, even when the final product is in the TG form [46].

The natural food matrix refers to the physical and chemical architecture of whole food in which nutrients and bioactive compounds are embedded [47]. At a fundamental level, the digestion and absorption of nutrients and their bioavailability are directly affected by the food matrix. Beyond this, interactions among nutrients, bioactives, and non-nutritive components provide properties distinct from those of individual constituents [48]. Hence, processing-induced changes in the endogenous components and overall nutrient profile can impact not only bioavailability but also downstream physiological responses [49].

We propose that these matrix-related effects are central to the omega-3 index changes observed in this study. Specifically, the concentrated omega-3 oil exhibited lower bioactivity than the whole fish oil derived from fresh salmon via protease enzyme hydrolysis. This process liberates the oil from muscle, brain, and ocular tissue, and as the enzymes lack lipase activity, the native TG structure and natural food matrix of the oil remain intact.

To further characterize the health profiles of the oils, their effects on commonly used systemic inflammatory markers, hsCRP, TNF-α, and IL-6 were assessed. Supplementation with both oils resulted in significant reductions in all three markers, with OmeGo demonstrating a greater numeric effect. At day 98, the relative reduction in hsCRP was 65% greater with OmeGo than the omega-3 comparator ($p<0.001$), while the reduction in TNF-α was 30% greater ($p<0.044$). A similar relative benefit was seen for IL-6, with a 50% greater reduction in the OmeGo group; this difference did not reach statistical significance ($p=0.133$). Overall, these findings suggest a meaningful effect of OmeGo, with a

consistent pattern of reductions across key biomarkers involved in systemic inflammation.

Inflammation is an essential process by which the body fights infections and repairs tissue damage, after which it normally returns to basal levels. However, when inflammation becomes chronic, it contributes to progressive tissue damage and an increased risk of long-term ill health. Chronic inflammation is associated with a wide range of disease states, including cardiovascular disease, obesity, and diabetes, and has been noted to progressively increase with age and has a positive correlation with chronic morbidity and reduced lifespan [50-53].

High-sensitivity CRP (hsCRP) is a well-established biomarker of increased CVD risk, and reductions in hsCRP are associated with improved CV outcomes [54]. TNF-α, CRP, and IL-6 are commonly raised in chronic conditions, including obesity, with higher levels associated with metabolic syndrome and poorer metabolic health, and the risk of developing diabetes [50-51].

Fish oil is generally considered to exert anti-inflammatory effects by providing O3 FAs, which are converted into resolvins, protectins, and maresins [55]. Fatty fish also contains other bioactive lipids with anti-inflammatory effects, including oleic acid (OA), which has been shown to reduce the expression of TNF-α and IL-6 [56]. OA also acts as a molecular decoy by binding highly inflammatory advanced glycation end products (AGEs), limiting their ability to promote inflammation and tissue damage [57]. Notably, OA is a principal constituent of olive oil, which occupies a central place in the Mediterranean diet and has been associated with improved health span and longevity [58]. Fatty fish also provides significant quantities of astaxanthin, a potent antioxidant that is estimated to be at least 50 times more active than vitamin E [59]. This is particularly notable in the context of the use of preservatives and additives to stabilise processed foods, which are associated with oxidative stress and a higher risk of chronic diseases [60]. Overall, while the O3I in individuals who regularly consume fish is likely to reflect the broader anti-inflammatory and antioxidant actions of natural fish oil, it is reasonable to question whether this biomarker has the same predictive value when the O3I is primarily driven by supplementation with a highly processed omega-3 supplement.

Nutrition and sleep are closely linked key pillars of health. Polyunsaturated fatty acids (PUFAs) support both the initiation and maintenance of sleep and serve as precursors for melatonin and serotonin [61-63]. The study recruited healthy participants and did not screen for pre-existing sleep disorders. Therefore, baseline sleep quality was expected to broadly reflect that of the general population. Despite this, a potential signal of improved objective sleep quality emerged in participants receiving OmeGo, with a 20% reduction in wakening events observed over the course of the study. In contrast, participants receiving the SSO3 exhibited a 20% increase in waking events. However, the between-group difference did not reach statistical significance, with both groups averaging around four waking events per night by study end.

It should be noted that wearable devices have lower sensitivity for distinguishing different phases of sleep compared to approaches such as polysomnography and are more likely to detect full awakenings rather than micro-arousals [64-65]. On this basis, both groups appeared to demonstrate sleep patterns consistent with those expected for their age group, and the apparent change in sleep quality might merely reflect natural fluctuations.

The enhancements in subjective sleep quality, assessed using the BNSQ, were included as an exploratory endpoint. No universal minimal clinical important difference (MCID) for the overall BNSQ has been established [32,66]. A study of sleepiness across different shift patterns in 84 men showed an overall score reduction of -1.24 points between the two shift types.

This change was associated with a significant decline of 8 mmHg in systolic blood pressure, suggesting a clinically relevant health benefit; however, the study was not randomised [67]. In the absence of definite data linking improvements in sleep quality, as assessed by the BNSQ, to improved health metrics, a reduction of ≥1.24 points was predefined as the minimally clinically relevant effect size. The changes over the duration of the study considerably smaller and therefore both groups were unlikely to have perceived any improvement in sleep quality. The trial recruited healthy participants; therefore, the limited changes observed in the sleep metrics would appear consistent with a healthy population.

The improvements in O3I and anti-inflammatory markers with OmeGo in the present study align with prior investigations examining the oil's natural bioactivity and the negative impact of processing. In a clinical study evaluating the impact of OmeGo on serum oxidised LDL-cholesterol (oxLDL-C) compared to two other omega-3 oils, the natural salmon oil produced a 2- to 4-fold greater reduction in oxLDL-C levels [27]. Supporting these findings, a preclinical study showed no additional benefit in lowering oxLDL-C when EPA and DHA levels were concentrated in OmeGo. In fact, exposing OmeGo to processing conditions commonly used in the manufacture of concentrated omega-3 oils, including heat treatment and exposure to oxygen, negatively impacted its capacity to reduce oxLDL-C. A second preclinical study demonstrated that this processing resulted in a loss of anti-inflammatory activity [68-69].

This trial has several limitations. First, it was of relatively short duration and recruited participants with an intermediate O3I. A longer-duration study would better reflect the benefits of sustained supplementation, while including participants with low baseline O3I would allow a better determination of the effects in those at greatest risk of adverse health outcomes associated with a low O3I. A longer study would also provide a clearer insight into the overall impact on inflammation and the relative health benefits of the interventions. In addition, assessing a broader panel of biomarkers would have provided a more comprehensive insight into other health effects, such as metabolic health (including blood glucose and insulin markers, and gastrointestinal health), as well as microbiome analyses. The design could also have been expanded to include other comparator oils, such as krill oil and omega-3 oils enriched with SPMs. Nevertheless, the study represents an important step in demonstrating the relevance of minimal processing and preservation of the natural food matrix to deliver health benefits that mirror those garnered from regularly consuming fish.

CONCLUSION

The results of this study indicate the importance of limited processing to replicate the health benefits of whole-food nutrition by supplementation. In this regard, a whole salmon oil, produced from the enzymatic hydrolysis of fresh salmon, increased the O3I and reduced key inflammatory markers in the blood to a significantly greater extent than a concentrated omega-3 oil despite the latter containing 2.5-fold more EPA and DHA (the fatty acids targeted in the O3I). Longer duration studies are warranted.

List of Abbreviations: AGEs, advanced glycation end products; BMI, body mass index; BNSQ, Basic Nordic Sleep Questionnaire; CHD, coronary heart disease; CVD, cardiovascular disease; DBS, dry blood spots; DHA, docosahexaenoic acid; EE, ethyl ester; EFA, essential fatty acid; EPA, eicosapentaenoic acid; FAMEs, fatty acid methyl esters; GC-FID, gas chromatography flame-ionization detection; HRV, heart rate variability; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; IRB, Institutional Review Board; MCID, minimally clinically important difference; O3 FA, omega-3 fatty acid; O3I, omega-3 index; oxLDL-C, oxidised low density lipoprotein-cholesterol; PUFA, polyunsaturated fatty acid; SSO3, Seven Seas Omega-3; TG, triglyceride; TNFα, tumour necrosis factor-alpha.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Competing Interest: C.C., C.B., and B.F. are consultants or employees of Hofseth BioCare, the study's sponsor. T.Å.M collaborates with Hofseth BioCare to support statistical planning and lead data analysis. C.C., C.B., and B.F. designed the study but had no role in the running of the study, including data collection, which was undertaken by Alethios, an independent company.

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