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Effectiveness of Omega-3 Fatty Acids Versus Placebo in Subjects at Ultra-High Risk for Psychosis: The PURPOSE Randomized Clinical Trial

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***Background and Hypotheses*: In the past 2 decades, substantial effort has been put into research on therapeutic options for people at ultra-high risk (UHR) for developing a first episode of psychosis (FEP), focusing on omega-3 polyunsaturated fatty acids (PUFAs) in preventing transition to psychosis. Despite an initial positive finding, subsequent studies failed to find a beneficial effect. The current study aimed to further investigate the effect of omega-3 PUFAs in UHR, to determine whether this line of research is worth pursuing.**

***Study Design*: A double-blind, randomized, placebo-controlled study testing the efficacy of 6-month treatment with omega-3 PUFAs in 135 subjects at UHR for FEP, aged 13 to 20 years on the prevention of a transition to psychosis, followed up for 18 months post-treatment. The trial was conducted at 16 general hospitals and psychiatric specialty centers located in 8 European countries and Israel.**

***Study Results*: There was no beneficial effect of treatment with omega-3 PUFAs compared to placebo; the rate of transition over 2 years did not differ between treatment arms nor was there a difference in change in symptom severity after 6-month treatment. Dropout rates and serious adverse events were similar across the groups.**

***Conclusions*: This is the third study that fails to replicate the original finding on the protective effect of omega-3 PUFAs in UHR subjects for transition to psychosis. The**

accumulating evidence therefore suggests that omega-3 PUFAs do not reduce transition rates to psychosis in those at increased risk at 2 years follow-up.
***Clinical Trials*: This trial is registered with ClinicalTrials.gov (NCT02597439; Study Details | Placebo-controlled Trial in Subjects at Ultra-high Risk for Psychosis With Omega-3 Fatty Acids in Europe | ClinicalTrials.gov).**

Key words: psychosis prevention/treatment/nutrition

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Introduction

Psychosis is typically preceded by a prodromal phase, where subthreshold psychotic symptoms are often accompanied by a decrease in psychosocial functioning.[1] This state poses a risk for developing psychosis, typically referred to as ultra-high risk (UHR).[2] Given that early treatment in psychosis has been linked to better outcomes,[3] effective interventions in the UHR phase may carry the potential to prevent or at least delay the onset of psychosis. Although meta-analyses in the past have suggested that cognitive behavioral therapy was associated with a significant reduction of attenuated psychotic symptoms compared to any other intervention,[4] more recent umbrella reviews and meta-analyses including new trials have indicated no clear benefits to favor any available intervention over another intervention or any control condition (eg, low-level needs-based interventions) in preventing psychosis, nor did any intervention show superior efficacy in the reduction of attenuated positive or negative symptoms, functioning or depressive symptoms.[5,6] These reports are in line with the Cochrane review, which concluded that "there was no convincing, unbiased, high-quality evidence to suggest that any type of intervention is of value" for subjects at clinical high risk for psychosis.[7]

One specific study that is part of these reviews and meta-analyses drew particular attention, concerning a randomized controlled trial (RCT) on the effectiveness of omega-3 polyunsaturated fatty acids (PUFAs) in UHR. This mono-center RCT by Amminger et al.[8] randomized 81 UHR subjects, aged between 13 and 25 years, 1:1 to 12-week treatment with omega-3 PUFAs or placebo. A lower transition rate to psychosis was found in the omega-3 group 1 year after study initiation (4.9% in the omega-3 group compared to 27.5% in the placebo group, $P = .007$), along with significantly reduced symptom severity and improved functioning, compared to placebo. Given the mild side effect profile of omega-3 PUFAs, they present an attractive option for preventative treatment in UHR subjects, especially compared to interventions such as antipsychotic medication with potential metabolic and extrapyramidal adverse effects, which are even more pronounced in children and adolescents.[9,10] However, the results by Amminger and colleagues were not replicated by 2 subsequent RCTs; first, the multicenter NEURAPRO trial, in which 304 subjects, aged between 13 and 40 years, were randomized 1:1 to a 6-month treatment with omega-3 PUFAs versus placebo, in addition to Cognitive Behavioral Case Management in both arms, found no differences in transition rates at one year after study initiation nor in symptomatic and functional improvement.[11] Recently, Qurashi and colleagues[12] conducted a trial in Pakistan, where 326 participants, aged between 16-35 years, were treated for 6 months with omega-3 PUFAs only, omega-3 PUFAs plus minocycline, minocycline only or placebo, followed by a 6-month observation period; the subjects treated with omega-3 PUFAs (with or without minocycline) had near-significant higher transition rate ($p = .07$) compared to subjects not treated with omega-3 PUFAs. Finally, a conference abstract based on the NAPLS data also reported the absence of a beneficial effect of PUFA over placebo on the transition rate in 118 UHR subjects who were treated for 24 weeks with an additional 18 months follow-up.[13] The current study further investigated the efficacy of omega-3 PUFA treatment versus placebo in preventing transition to psychosis, in an adolescent UHR sample recruited across Europe and Israel.

Methods

Study Design and Setting

The Placebo-controlled trial in subjects at Ultra-high Risk for Psychosis with Omega-3 fatty acidS in Europe (PURPOSE) trial is a double-blind, randomized, placebo-controlled study testing the efficacy of a 6-month treatment with omega-3 PUFAs in subjects at UHR for psychosis, followed up for 18 months post-treatment. The trial was conducted at 16 general hospitals and psychiatric specialty centers located in 8 European countries and Israel and was approved in each country by the respective regulatory authorities and ethics committees. The University Medical Center Utrecht, Netherlands, monitored the trial according to Good Clinical Practice and the International Conference on Harmonization guidelines (ICH-GCP).[14] The safety of the study was annually monitored by an independent Data Safety Monitoring Board.

Aged between 13 and 20 years, participants were help-seeking individuals who met UHR criteria on the positive symptoms of the Comprehensive Assessment of At-Risk Mental States (CAARMS), including a 30% drop in Social and Occupational Functioning Assessment Scale (SOFAS) score from premorbid level, sustained for a month and occurred within past 12 months OR SOFAS score of 50 or less for past 12 months or longer.[15] These criteria are commonly applied in UHR research.[15] The most important exclusion criteria were as follows (full list in Supplementary Section A): current or past DSM-IV diagnosis of a schizophrenia-spectrum disorder; intake of an antipsychotic or mood-stabilizing agent within 2 weeks before study enrollment; intake of an antipsychotic equivalent to a total haloperidol dose of >50 mg in the 6 months prior to enrollment; more than 4 weeks of regular omega-3 supplementation within the last 6 months. All study participants (or their legal representatives in case of minors) provided written informed consent. As not to withhold any treatment, participants were allowed to continue or initiate treatment as usual (detailed overview of used therapy at baseline (ever and current) as well as throughout the study provided in Supplementary Section I). This trial is registered with ClinicalTrials.gov (NCT02597439). The protocol amendments are described in Supplementary Material.

Randomization

Subjects were randomized to omega-3 PUFAs or placebo in a 1:1 fashion. A randomization sequence (A versus B) was generated by the Clinical Trial Center of the University of Zürich, Switzerland, which was used to label the study medication. Randomization, stratified by site and gender, was completed through a randomization module built into the Electronic Data Capture system, using block randomization. Randomization was performed by the local study team. All study team members (local and central) as well as the participants were blind to treatment allocation assigned by the randomization module.

Study Intervention

The active treatment was a supplement of 0.6-g yellow gelatin capsules containing concentrated marine fish oil, administered orally. The daily dose of 4 capsules provided 720 mg of eicosapentaenoic acid (EPA; 20:5n3), 480 mg of docosahexaenoic acid (DHA) (22:6n3), and 7.6 mg of mixed tocopherol (vitamin E). The daily amount of other omega-3 fatty acids (18:3n3, 18:4n3, 20:4n3, 21:5n3, and 22:5n3) provided with the study medication was 240 mg. Placebo capsules were matched to the fish oil capsules in size, appearance, and smell. The composition of the capsules was almost identical to the ones used in the trial conducted by Amminger et al.,[8] who used a daily dose of 700 mg of EPA instead of 720 as used in the current trial.

Outcomes

The primary aim of this RCT was to compare the rate of transition to psychosis between individuals at UHR for psychosis and randomized to omega-3 fatty acids to those randomized to placebo, throughout the 2-year study period. The CAARMS criteria were used to assess the transition to psychosis. Importantly, as a secondary objective, the definition of transition to psychosis was extended to also include subjects who exceeded the maximally allowed dose of antipsychotics during the study (ie, equivalent of a total haloperidol use of 10 mg within 2 months). This extended definition was included to capture potentially 'hidden' transitions: in theory, a subject could first meet UHR criteria on the CAARMS, subsequentially experience a worsening of symptoms for which a clinically effective antipsychotic treatment is prescribed, leading to a sufficient dampening of symptoms to avoid meeting 'transition' criteria on the CAARMS. Other secondary objectives included comparisons between the 2 treatment arms over the 2-year study period regarding discontinuation rate and tolerability, comparisons on symptomatology, global functioning, and quality of life. A complete overview of the study procedures is provided in eTable 1. After the baseline visit, when randomization and medication initiation occurred, follow-up assessments were performed at 1 month, 3 months, 6 months (end of treatment), 1 year, 1.5 years, and 2 years post-baseline. Transition to psychosis was assessed every 6 months using the CAARMS criteria. CAARMS raters were experienced clinicians who were extensively trained in the administration of outcome measures, requiring certification before their involvement in the study. During the required exam for certification, all raters correctly scored fictive subjects as meeting versus not meeting CAARMS criteria, leading to an intraclass correlation coefficient of 1. Study medication adherence was assessed using bioactive blood levels at baseline and end of treatment; EPA, DHA, and the omega-3 index were used as an objective measure of treatment adherence. The exact method used to quantify the composition of erythrocyte fatty acids is provided in Supplementary Section D.

Statistical Analysis

Power analysis indicated that 170 subjects were required in order to detect a relatively conservative 70% reduction in the expected transition rate at 1 year of follow-up,[8] thus corresponding to a transition rate of 22% in the placebo group and 6.6% in the omega-3 group, using a 2-sided log-rank test with $\alpha = .05$ (probability of type I error) and 80% statistical power ($\beta = .2$, probability of type II error).[16] Given the long duration of both treatment and follow-up we anticipated a dropout rate of 20% to 30%, which resulted in the overall required inclusion of 220 subjects in the current study. Of note, these calculations

are based on a treatment of 12 weeks,[8] whereas our study includes 6 months of treatment.

The primary outcome of this study, the time to psychosis, was determined by subtracting the date of the baseline visit (randomization) from the date of transition to psychosis. In case no transition to psychosis occurred, the date of the baseline visit (randomization) was subtracted from the date of the last study visit. To model the effect of treatment on time until psychosis, Cox regression was used. To test for a difference in dropout rates between the 2 treatment arms, Chi-square tests were performed. Furthermore, Cox regression was used to determine the effect of treatment on time to dropout. Time to dropout was determined by subtracting the start date of the follow-up period from the date of dropout; in case no dropout occurred, the start date was subtracted from the date of the last study visit. For all participants, all dates were available, so there were no missing values for the primary outcome. To test for differences between the 2 treatment arms, a 2-sided level of significance of 5% was used. Kaplan–Meier curves with 95% confidence intervals were created based on the Cox regression results. As descriptive statistics, means, and standard deviations are included for the continuous variables, percentages are included for the categorical variables. The primary analyses are conducted on a modified Intent To Treat sample (mITT), meaning that subjects who were found to be ineligible after randomization was completed, were excluded. Sensitivity analyses are conducted in the full ITT sample (Section F in Supplementary Material). As secondary outcomes of this study questionnaires for global functioning and quality of life were conducted longitudinally: Positive And Negative Syndrome Scale (PANSS),[17] Beck's Depression Inventory (BDI),[18] SOFAS,[19] Global Functioning: Social (GF:S; Auther et al., 2006),[20] Global Functioning: Role (GF:R; Niendam et al., 2006)[21] and Young Mania Rating Scale (YMRS).[22]

If a questionnaire was incomplete with 80% or more of the questions answered, missing data were imputed by using the average of the answers available from that questionnaire for that individual. If less than 80% of an individual questionnaire was completed or was completely missing, the questionnaire was treated as missing. Mixed effects models were used to analyze the patterns of the secondary outcomes over time and to test whether these patterns differed between the 2 treatment arms. These models account for the correlation of repeated measurements within a patient and allow for the estimation of effects in case a questionnaire is missing over time. A normal distribution was used to model the outcome variables. Due to the non-linear trend in the data, "time" as well as "time^2" were included as fixed effects. In order to compare treatment arms, "treatment" as well as "treatment X time interaction" was added as a fixed effect. A random intercept per patient was used to account for repeated measures. All analyses were performed in R Statistical Software (version 4.2.2).[23]

Results

Subjects were recruited between September 30, 2015, and December 31, 2020, with the final study visit taking place on February 1, 2023. The CONSORT diagram is shown in **Figure 1**. A total of 158 subjects signed the informed consent and were assessed for eligibility; 12 subjects failed during the screening visit (8%), resulting in 146 randomized subjects. Of these subjects, another 11 (8%) were excluded from the analyses due to not meeting eligibility criteria; the annual on-site eligibility check by the study monitor often occurred after the subject was already randomized. For 9 of these 11 subjects, exclusion criteria were present in the medical files (which are not accessible remotely); for the remaining 2 subjects, source documentation for the assessments to confirm eligibility was not present on-site. One hundred and thirty-five subjects met diagnostic criteria; 75 women and 60 men were included with a mean age (SD) of 15.6 (SD 1.8); 86% of the study sample was white. Baseline characteristics are shown in **Table 1**; there are no clinically meaningful imbalances between treatment arms. Of the 135 subjects, 117 (87%) completed the 6-month treatment and 92 (68%) completed the 18-month follow-up period after treatment was completed. The trial was prematurely terminated due to slow enrollment mainly caused by the COVID pandemic, decreasing the power of the analyses.

The primary analyses were conducted in the modified Intent To Treat (mITT) sample (n = 135). In the omega-3 PUFA treatment group, 5 (7.5%) of 67 subjects met the strict transition criteria over the full 2-year study period, versus 3 (4.4%) of 68 placebo-treated subjects (however, the outcome measure was only available for n = 46 in the PUFA group, vs. n = 46 for the placebo group). The Cox regression analysis showed that the transition rate did not differ between the 2 treatment groups (HR 1.67, 95% CI: 0.40;6.98, P-value = .5). Similar results were found when applying the more extensive transition definition: in the omega-3 PFUA treatment group, 16 (23.9%) of 67 subjects met these criteria, versus 8 (11.8%) of 68 placebo-treated subjects. The transition rate did not differ (HR 1.88, 95% CI, 0.79;4.49, P-value = .2). Results are provided in **Figures 2** A and B.

Strict definition: transition as per the CAARMS criteria. Extended definition: transition as per the CAARMS criteria and/or exceeding the maximally allowed dose of antipsychotics during the study (ie, equivalent of a total haloperidol use of 10 mg within 2 months).

The duration of follow-up was longer than 2 years in a few subjects due to COVID-19 pandemic-related restrictions in site visits. The discontinuation rate did not differ between treatment arms (Supplementary eFigure 1). The primary analyses were repeated in the full ITT sample with

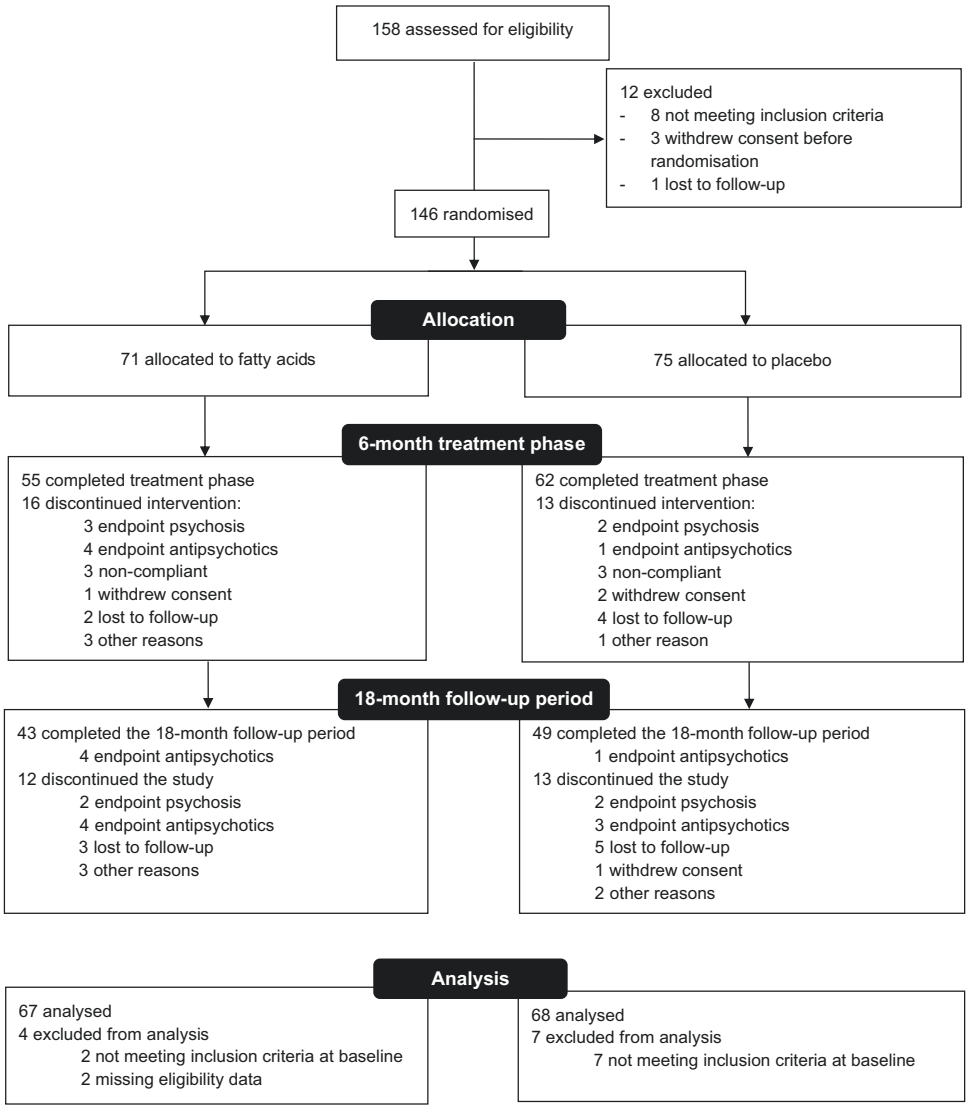

Figure 1. CONSORT subject flowchart PURPOSE trial.

similar outcomes as the mITT analyses (Supplementary eFigure 2A/B). **Table 2** provides the results of the fixed effects of the models fitted on the longitudinal data; with the exception of the YMRS score, there was a significant effect of time on all of the scores. However, there were no differences regarding the change in symptom severity on the various assessment scales between the 2 treatment groups, nor were there significant treatment arm X-time interactions.

Baseline and end-of-treatment blood samples to measure adherence were available for 96 subjects, 48 subjects in each treatment arm. Results are presented in Supplementary eTable 2, indicating that the subject sample randomized to omega-3 PUFAs had a significant increase in omega-3 PUFA levels from baseline to end of treatment; an effect that was absent in subjects randomized to placebo. Concomitant medication used at baseline, during the treatment phase and during the follow-up is presented in **Table 3**; most importantly, 38.8% of omega-3 subjects and 33.8% of placebo-treated subjects used antidepressants during the treatment phase.

The number of adverse events was low in both groups, with only 4 events reported in 5% or more of the subjects within one or both of the individual treatment arms during the treatment phase: common cold, influenza, nausea, and suicidal ideation. The latter was reported in 6 subjects (9%; Serious Adverse Event [SAE] criteria were met for 2 subjects) randomized to omega-3 versus 7 subjects (10%; SAE criteria were met for one subject) in the placebo arm (full overview of adverse events reported in Supplementary eTable 3). In total, 37 SAEs occurred in 28 unique subjects who were eligible for the study, in the period between randomization and the end of the study. Of these, 19 SAEs occurred in 15 subjects randomized to the active treatment arm; 17 hospitalizations (10 psychiatric in nature) and 2 pregnancies. A total of 18

Table 1. Baseline Demographic and Clinical Characteristics.

	Omega-3 arm (*n* = 67)	Placebo arm (*n* = 68)
Age (years; mean SD)	15.8 (1.7)	15.5 (1.8)
Sex (*n*; %)		
-Female	37 (55.2)	38 (55.9)
-Male	30 (44.8)	30 (44.1)
Ethnicity (*n*; %)		
-White/European descent	58 (86.6)	58 (85.3)
-African descent	2 (3.0)	0 (0)
-East Asian descent	2 (3.0)	0 (0)
-Asian Indian descent	1 (1.5)	0 (0)
-Middle Eastern descent	1 (1.5)	3 (4.4)
-Other	3 (4.5)	9 (13.2)
IQ (mean; SD)	98.1 (17.7)	101.0 (18.5)
CAARMS subgroups (n; % - multiple options possible)		
Attenuated psychosis	57 (85.1)	62 (91.2)
Family history	20 (29.9)	19 (27.9)
BLIPS	2 (3.0)	1 (1.5)
Major Depressive Disorder (current)[a] (*n*; %)	36 (53.7)	32 (47.1)
Substance abuse and/or dependence in past 12 months [a] (*n*; %)	4 (6.0)	5 (7.4)
PANSS total score (mean; SD) [b]	59.0 (13.8)	60.2 (15.1)
PANSS positive subscale (mean; SD) [b]	13.0 (3.3)	12.8 (3.1)
PANSS negative subscale (mean; SD) [b]	14.0 (5.2)	14.7 (5.9)
PANSS general subscale (mean; SD) [b]	32.0 (8.3)	33.0 (9.0)
Beck's Depression Inventory score (mean; SD)[c]	25.2 (15.6)	25.0 (15.4)
Young Mania Rating Scale score (mean; SD)[d]	2.2 (2.7)	2.5 (3.1)
Global Functioning: Social (mean; SD)[e]	6.0 (1.1)	6.1 (1.3)
Global Functioning: Role (mean; SD) [e]	6.1 (1.4)	6.3 (1.2)
SOFAS (mean; SD)[f]	53.1 (9.0)	55.3 (9.9)

Data are *n* (%) or mean (SD). Denominators change due to incomplete data. Some variables allowed the selection of more than one answer option.
CAARMS, Comprehensive Assessment of At-Risk Mental States; PANSS, Positive and Negative Syndrome Scale; SOFAS, Social and Occupational Functioning Scale.
[a]According to the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL).
[b]Theoretical scores range from 30 to 210 (total scale), 7-49 (positive scale), 7-49 (negative scale), 16-112 (general psychopathology scale). Higher scores indicate more severe psychopathology.
[c]Theoretical scores range from 0 to 63. Higher scores indicate greater severity of illness.
[d]Theoretical scores range from 0 to 60. Higher scores indicate greater severity of illness.
[e]Theoretical scores range from 1 to 10. Higher scores indicate better functioning.
[f]Theoretical scores range from 0 to 100. Higher scores indicate better functioning.

SAEs occurred in 13 subjects in the placebo arm, all hospitalizations (13 psychiatric in nature).

Discussion

After a 6-month treatment with omega-3 PUFAs and over an additional 18-month follow-up period, the transition rate to psychosis in a sample of subjects at UHR for psychosis was not reduced compared to placebo. This finding remained consistent even when a slightly more liberal definition of 'transition' was applied, including subjects who exceeded the maximally allowed dose of antipsychotics during the study, suggesting a transition to a psychotic disorder. No differences were found between the treatment groups regarding changes in symptom severity.

Our findings are in line with the reports by McGorry[11] and Qurashi,[12] but in conflict with the results from Amminger.[8] The initial positive finding by the latter is challenging to explain in light of the accumulating negative findings. Various factors, such as improvements in UHR non-pharmacological treatment over time, the use of comedication, endpoint definitions, the composition of study medication and the illness severity of the sample, may contribute to this discrepancy. First, the non-pharmacological treatment of UHR symptomatology may have become more effective in the past decade, which could lead to less room for symptom improvement for additional interventions. A decline in transition rates has been reported consistently,[24] which is mirrored by the difference in transition rates in the positive trial (16% over a period of one year)[5] compared to the far lower rate in the current study (3.7% and 5.9% over a 2-year period, depending on the definition of transition). A study by Formica and colleagues[25] included

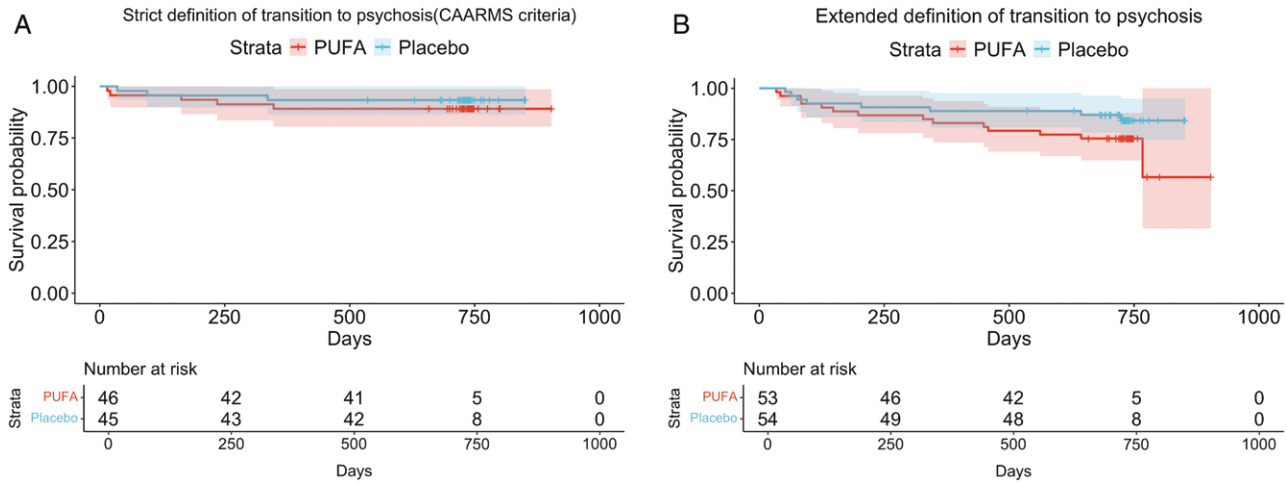

Figure 2. The rate of transition to psychosis was compared between subjects treated with omega-3 Polyunsaturated Fatty Acids (PUFA) and placebo, applying a strict definition of transition (A) and an extended definition of transition (B).

UHR subjects coming into care between 1995 and 2006; a decrease in transition rates over this period was demonstrated, in parallel to an increase in the number of sessions with therapists, more cognitive behavioral therapy and more psychoeducational sessions focused on problem-solving for UHR subjects. The relationship between the year when subjects came into care and the transition rate disappeared when the increases in non-pharmacological treatment were adjusted for. The negative studies on omega-3 PUFA effectiveness did present substantially lower transition rates compared to the positive study, possibly caused by a ceiling effect due to the effects of non-pharmacological treatments, leaving less room for improvement associated with omega-3 PUFA treatment. In addition, it is possible that the inclusion of adolescents ages 13-17 at UHR could have reduced the transition rate to psychosis. Rates of transition to psychosis in pediatric UHR samples have been lower than in samples consisting (predominantly) of adults. In a recent meta-analysis of individuals aged 9 to 18 years fulfilling criteria for UHR, cumulative transition rates were 9.5% (95% CI = 5.5%-14.2%) at 1 year, 12.1% (95% CI = 6.7%-18.6%), at 2 years, and 16.1% (95% CI = 5.6%-30.0% at ≥5 years).[26] These transition rates are considerably lower than those reported in a recently updated meta-analysis of predominantly adults at UHR, where the cumulative transition rates were 15% (95% CI = 13%-16%) at 1 year, 19% (95% CI = 17%-22%) at 2 years, and 28% (95% CI = 20%-37%) >4 years.[27] Possible explanations for lower transition rates to psychosis in pediatric UHR samples have been discussed and focused especially on the potentially lower specificity of attenuated positive symptoms, particularly of perceptual abnormalities, at a developmental stage where other psychiatric disorders with potentially overlapping psychopathology emerge, including mood disorders, personality traits, and disorders, obsessive-compulsive disorders.[28–31]

In addition, the different studies report striking differences in the use of comedication, specifically antidepressant use. While the trial by Amminger reported antidepressant use in only 9.9% of participants,[8] in our study the frequency is considerably higher at 35%, with even greater use in the study by McGorry[11] at 62%. A systematic review and meta-analyses on 16 naturalistic, observational, and cohort studies including 2.182 subjects concluded that ongoing exposure to antidepressants once UHR status is established, is associated with a reduced risk for transition to psychosis at follow-up.[32] This finding may be relevant to the variety in transition rates for the omega-3 PUFA studies, given that the trials with higher antidepressant use (McGorry[11] and the current trial) also found lower transition rates. Higher transition rates result in more power to detect differences between treatment arms. Due to the lower transition rates, our current study as well as the other negative studies provided less power to detect a difference.

The third potential factor explaining the positive finding in the face of 3 negative studies, is a different definition of the endpoint across trials. While all negative studies used the CAARMS or SIPS, which are commonly administered to both assess UHR status as well as transition to psychosis, Amminger et al. used the PANSS, which is used to assess symptom severity in patients with schizophrenia-spectrum disorders. However, it has been demonstrated that the PANSS showed good convergent validity with the CAARMS composite score,[33] arguing against this as a potential cause for the deviant results. Similarly, any differences in the composition of study medication as a potential cause for the conflicting results can be ruled out, as the composition was very similar across trials.

Finally, it is possible that differences in illness severity could have driven the conflicting results observed. The total PANSS score at baseline was only reported by

Table 2. Results of the Mixed Model Analysis of the Several Questionnaire Scores.

	Time	Time^2	Group [a]	Interaction group × time
PANSS total score [b]				
Estimate	−0.234	0.0071	0.275	
95% CI	(−0.316; −0.152)	(0.0039; 0.010)	(−1.363; 1.888)	
P-value	<.0001	<.0001	.739	.251
PANSS positive subscale score [b]				
Estimate	−0.228	0.0066	−0.322	
95% CI	(−0.291; −0.165)	(0.0041; 0.0091)	(−1.230; 0.577)	
P-value	<.0001	<.0001	.484	.552
PANSS negative subscale score [b]				
Estimate	−0.234	0.0072	0.275	
95% CI	(−0.316; −0.152)	(0.0039; 0.0104)	(−1.363;1.888)	
P-value	<.0001	<.0001	.739	.385
PANSS general subscale score [b]				
Estimate	−0.640	0.018	−0.040	
95% CI	(−0.764;−0.518)	(0.013; 0.023)	(−2.158; 2.066)	
P-value	<.0001	<.0001	.970	.242
Beck's Depression Inventory Score [c]				
Estimate	−0.995	0.029	−0.113	
95% CI	(−1.252; −0.738)	(0.019; 0.040)	(−4.512; 4.285)	
P-value	<.0001	<.0001	.960	.906
Young Mania Rating Scale score [d]				
Estimate	0.0020	−0.0008	0.034	
95% CI	(−0.059; 0.010)	(−0.0041; 0.0025)	(−0.670; 0.744)	
P-value	.615	.621	.925	.225
Global Functioning: Social score [e]				
Estimate	0.096	−0.0027	0.194	
95% CI	(0.073; 0.118)	(−0.0036; −0.0018)	(−0.190; 0.578)	
P-value	<.0001	<.0001	.322	.701
Global Functioning: Role score [e]				
Estimate	0.084	−0.0019	0.263	
95% CI	(0.059; 0.108)	(−0.0029; −0.0010)	(−0.152; 0.676)	
P-value	<.0001	<.0001	.215	.224
SOFAS score [f]				
Estimate	1.368	−0.038	2.279	
95% CI	(1.127; 1.609)	(−0.047; −0.028)	(−1.136; 5.690)	
P-value	<.0001	<.0001	.192	.371

[a]The group effect is the mean difference between the patients in the Placebo arm and the Omega-3 arm
[b]Theoretical scores range from 30 to 210 (total scale), 7-49 (positive scale), 7-49 (negative scale), 16-112 (general psychopathology scale). Higher scores indicate more severe psychopathology.
[c]Theoretical scores range from 0 to 63. Higher scores indicate greater severity of illness.
[d]Theoretical scores range from 0 to 60. Higher scores indicate greater severity of illness.
[e]Theoretical scores range from 1 to 10. Higher scores indicate better functioning.
[f]Theoretical scores range from 0 to 100. Higher scores indicate better functioning.

Amminger (57.2 and 59.9 in the placebo vs active group) and the current study (60.2 and 59.0, respectively), indicating a similar level of symptom severity. When comparing the classifications of the various functioning scale scores between the trials, the 5 study samples all score "moderate difficulty with functioning" at baseline.

In summary, none of the factors that could potentially explain the initial positive findings in contrast to the 3 negative trials is sufficiently convincing. With the majority of the RCTs demonstrating no beneficial effect of omega-3 PUFA, its broader clinical use to prevent the progression of mental disorders in UHR states should not be promoted to avoid any delay for more effective preventive strategies.

Some limitations to the current study need to be taken into account. First, the daily intake of PUFAs through regular diet was not measured, nor can the use of non-study omega-3 supplements be excluded. This, in combination with a lower transition rate than expected as well as the premature termination leading to an underpowered sample, has impacted the power of our analyses, limiting our abilities to draw solid conclusions. Another limitation concerns the absence of a risk enrichment method, such as a polygenetic or polyenvironmental prediction model, in our subject screening, which potentially would have increased transition rates. The participating centers were hospitals and specialty centers, who mostly recruited subjects through their daily clinical practice, meaning

Table 3. Concomitant Medication Used During the Study, Per Treatment Arm.

	Omega-3 arm	Placebo arm
Antidepressants (%; *n*)		
At baseline	28,4% (19/67)	23.5% (16/68)
During treatment phase	38.8% (26/67)	33.8% (23/68)
During follow-up phase	58.2 (32/55)	45.2% (28/62)
Antipsychotics (%; *n*)		
At baseline*	0% (0/67)	4.4% (3/68)
During treatment phase	16.4% (11/67)	14.7% (10/68)
During follow-up phase	30.9% (17/55)	24.2% (15/62)
Benzodiazepines (%; *n*)		
At baseline	7.5% (5/67)	4.4% (3/68)
During treatment phase	13.4% (9/67)	10.3% (7/68)
During follow-up phase	16.4% (9/55)	12.9% (8/62)

*Antipsychotics at baseline were only allowed when prescribed in low doses (noneffective dosages for the treatment of psychosis) with the indication for use of sleep problems or anxiety. Subjects who exceeded the maximally allowed dose of antipsychotics during the study (ie, equivalent of a total haloperidol use of 10 mg within 2 months) were withdrawn from the trial.

that the vast majority of the recruited subjects were help-seeking individuals. However, two of our participating centers have recruited through General Practitioner offices, advertisements, and schools. Although these specific centers were also recruited through their daily clinical practice, a maximum of 18 subjects may be recruited through this more broad recruitment approach.

In conclusion, our findings confirm previous evidence that disputes the initially reported beneficial effect of omega-3 PUFA in the prevention of transition to psychotic disorders in subjects at UHR for psychosis. The cumulative evidence from 3 international, large-scale studies demonstrating a lack of any protective effects of omega-3 on the transition to psychosis argues against future studies in this line of research and does not support its promotion as a preventive treatment option in UHR states for psychosis.

Supplementary material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Conflict of interest

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request, as is the study protocol.

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