NEURAPRO: A Multi-Centre RCT of Omega-3 Polyunsaturated Fatty Acids versus Placebo in Young People at Ultra-High Risk of Psychotic Disorders

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Abstract

Importance

Since the operationalization of the clinical criteria indicating an ultra-high risk for psychotic disorder over two decades ago, a number of interventions have been trialled, with the aim of preventing onset of psychotic disorder and improving outcomes. Among the most promising has been dietary supplementation with long-chain omega-3 polyunsaturated acids (PUFA), which in a single-centre study involving 81 participants, was shown to significantly reduce the risk of transition to psychosis over a 12-month period, as well as improving symptomatic and functional outcomes, an effect that persisted long-term (median 6.7 years). The current trial aimed to replicate these findings in a large-scale multi-centre study.

Objective

To determine whether treatment with PUFA, in combination with a high-quality psychosocial intervention, cognitive behavioural case management (CBCM), is more effective than placebo plus CBCM in preventing transition to psychosis and improving outcomes in young people at ultra-high risk for psychosis.

Design, setting and participants

A randomized, double-blind, placebo-controlled trial was conducted in 10 specialized early psychosis treatment services in Australia, Asia, and Europe, involving a total cohort of 304 participants.

Interventions

The intervention consisted of a daily dose of 1.4 g omega-3 PUFA or placebo (paraffin oil), plus up to 20 sessions of CBCM over the 6-month study period.

Main outcomes and measures

The primary outcome was transition to psychosis status at 6 months, as defined by the CAARMS. The secondary outcomes were general levels of psychopathology and functioning, as assessed by the BPRS, SANS, MADRS, YMRS, SOFAS and the Global Functioning: Social and Role scales.

Conclusions and relevance

This trial failed to replicate the findings of the original single-centre trial, principally due to the lower than expected transition rate and a substantial improvement in outcome in both groups. No difference was observed between the transition rates of both groups, which is consistent with omega-3 PUFAs lacking any efficacy. However, the low transition rate clearly inhibited our ability to test the main hypothesis that omega-3 PUFAs are effective in reducing the risk of first episode psychosis. The low transition rate could be because the sample was insufficiently enriched, or more likely, that the other treatments received

produced a ceiling effect, beyond which omega-3 PUFAs did not confer additional benefits. Further analysis and additional research is necessary to enable definitive conclusions to be drawn.

Trial Registration

Australian New Zealand Clinical Trials Registry ACTRN 12608000475347

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Psychotic illnesses, and especially schizophrenia, typically emerge from initially subtle and relatively non-specific symptoms, building through a prodromal period of sub-threshold positive symptoms to cross a somewhat arbitrary threshold that enables a first episode of psychosis to be diagnosed.[1] The operational definition of the "at-risk" or "ultra-high risk" (UHR) mental state, [2, 3] which prospectively identifies people at incipient risk of progression to full-threshold psychosis, has catalyzed an intense research effort as well significant reforms to clinical care. These patients are typically distressed, functionally impaired and manifest a need for clinical care on the basis of their current symptoms, in addition to the potential benefit of reducing the risk for progression to psychosis.[4, 5] A series of research studies has now validated the UHR criteria and enabled the study of a range of treatment strategies to relieve distress, improve functioning and reduce the risk for progression to a psychotic illness.[2, 3, 6-14]

To date, 11 trials assessing psychosocial or pharmacological interventions, alone or in combination, have been carried out in UHR cohorts. A recent meta-analysis of these trials has shown that these interventions are effective, with an overall risk reduction of 54% at 12 months, with a NNT of 8 (4–13).[15] All treatments in these studies appeared to reduce the risk of progression to psychosis, at least during the first 6–12 months. In line with the clinical staging model of illness,[16-20] during the earliest stage of illness, safer interventions, such as long-chain omega-3 polyunsaturated fatty acids (PUFA) and cognitive behavioural therapy (CBT), should be regarded as the preferred option for first-line treatment. CBT, a well-established and safe psychosocial intervention, adapted for this stage of illness, has been found to be effective in many, though not all, of the published trials.[21-26] However, the most striking result from the trials to date was the finding that omega-3 PUFA were greatly superior to placebo in reducing the risk for transition to psychosis, and psychiatric morbidity in general, not only during the period of treatment, but for a prolonged period (median 6.7 years) subsequently.[27, 28] Omega-3 PUFA are safe, beneficial to health in many ways, and represent a simple and relatively inexpensive potential treatment strategy. The initial omega-3 study was therefore clearly worthy of attempted replication.

Methods

Study design and setting

This was a randomized, double-blind, placebo-controlled 6-month treatment trial of omega-3 PUFA, followed by an additional 6-month follow-up period, in 304 participants who received either omega-3 PUFA together with cognitive behavioural case management (CBCM), or placebo with CBCM. The total study period was 12 months. Assessments were made at baseline, 6 and 12 months after trial entry. In addition, assessments of psychopathology were conducted monthly during the first 6 months and also at Month 9. The 6 and 12-month results are presented here. The study was performed in accordance with the Declaration of Helsinki and is consistent with ICH Good Clinical Practice.[29] The National Health and Medical Research Council of Australia National Statement on Human Research was also adhered to, and appropriate

ethical approval was obtained by each site, and any local regulatory requirements met before the trial commenced. For complete details of the study methodology, see Markulev et al.[30]

Help-seeking individuals attending the trial centres were eligible to participate if they were aged 13–40 years and met criteria for one or more of the UHR groups: attenuated psychotic symptoms, transient psychosis, or genetic risk. In a variation to our previous UHR intervention studies, all participants either had a low level of functioning (SOFAS < 50) sustained for at least a year or had experienced a significant decrease in their functioning (a 30% or greater reduction in their SOFAS score) over the past year.[31] Participants were required to be able to give informed consent. Exclusion criteria included a previous psychotic episode of 7 days or longer, current symptoms due to acute intoxication, organic brain disease, serious developmental disorder, abnormal coagulation profile or thyroid function, physical illness with a psychotropic effect, current treatment with mood stabilizers, past neuroleptic exposure to a total lifetime haloperidol equivalents dose of >50 mg, IQ of <70, dangerous behaviour, aggression or suicidality, pregnancy, or current supplementation with omega-3 PUFA.[30]

Randomization

Participants were randomized at study entry to either the omega-3 PUFA plus CBCM group, or the placebo plus CBCM group via an online electronic data management system. Randomization was stratified by site and total score on the Montgomery-Asberg Depression Rating Scale (MADRS),[32] as both depression and antidepressants may impact on UHR symptoms and illness progression.[33-36] All participants, those involved in delivering interventions, assessing outcomes and data entry were blind to group assignment. The trial statistician (HPY) was unblinded at the analysis stage.

Study interventions

Participants received either omega-3 PUFAs or placebo together with clinical care with CBCM for the 6-month intervention phase, after which both the omega-3 PUFAs and placebo were ceased, although patients could continue to access CBCM on the basis of need throughout this 6-month follow-up.[30] A total of 125 participants continued to receive CBCM after the 6-month follow-up visit, with a mean of 4.1±3.71 (range 1–16) sessions attended.

For the first 12 months of the study, antidepressants (SSRIs only) were permitted for moderate–severe major depression (MADRS score ≥21 for at least two consecutive weeks), and benzodiazepines were permitted for anxiety. The use of antipsychotics or mood stabilizers was not permitted at any time during the trial unless a participant was withdrawn from the study prior to 12 months and these treatments were deemed necessary according to clinical guidelines.

The study medication comprised a daily dose of four gelatine capsules throughout the 6-month treatment period. Participants were dispensed bottles of capsules, with each capsule containing either: (i) 0.650–

0.750 g concentrated marine fish oil (active intervention; containing 840 mg EPA and 560 mg DHA or approximately 1.4 g omega-3 PUFAs/day); or (ii) 0.650–0.750 g of paraffin oil (placebo intervention). This dose was similar to that in our previous study.[27]

Outcome measures

The primary outcome was transition to psychosis status at 6 months, with transition defined on the basis of operationalized criteria and assessed with the Comprehensive Assessment of the At-Risk Mental State (CAARMS).[31] Diagnoses (both psychotic and non-psychotic) were determined with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, and the secondary measures included the BPRS,[37] SANS,[38] MADRS,[32] YMRS,[39] SOFAS[40] and the Global Functioning: Social and Role scales.[41]

Adherence to the study medication was assessed monthly for each participant based on capsule count. The average adherence rating over the 6-month intervention period was then computed and categorized as either adherent, with ≤25% of capsules returned, or non-adherent, with >25% of capsules returned. Adverse events and serious adverse events were monitored throughout the study, and were assessed at each visit during the intervention phase and classified into categories for further analysis.

Statistical analysis

The study was powered to detect a 13% difference in the transition rates between the two treatment groups, with the 6-month transition rate in the placebo group assumed to be 15%.[30] The primary analysis used the intention-to-treat (ITT) approach and compared the difference in transition rates between the treatment groups using survival analysis with the stratified log-rank test and Cox regression with recruitment site and baseline MADRS score (<21 and ≥21) used as stratifying factors. General linear modelling and linear mixed effects model analysis were used to compare the secondary outcomes (symptomatology and functioning) for the two groups. Further analysis to compare the treatments was conducted by taking adherence into account for both the primary and the secondary outcomes.

Risk class analysis was also undertaken using demographic characteristics (age, gender, race, years of education, duration of untreated symptoms) and symptom and functioning measures (BPRS, SANS, MADRS, YMRS, SOFAS, global functioning) as potential risk factors, to identify a subgroup of patients who might be at a relatively higher risk of transition. The two treatments were then compared within this subgroup in terms of the primary and secondary outcomes using the above-mentioned statistical methods.

Results

Study sample

The study cohort consisted of 304, with 153 randomly assigned to omega-3 PUFA treatment and 151 to placebo. The baseline characteristics of both groups were similar (Supplementary Tables 1 and 2). Fourteen of the 153 (9.1%) particpiants from the omega-3 group, and 18/151 (11.9%) from the placebo group discontinued the intervention prematurely (i.e., prior to 6 months). Twenty-four (15.7%) participants from the omega-3 group were unable to be contacted and one became pregnant, while 22 (14.6%) participants were unable to be contacted from the placebo group, meaning that in total 79 (26%) participants were lost to follow-up (Figure 1). The mean duration of untreated illness was 891.1 days (median 467, SD 969.1 days) in the omega-3 group and 897.6 days (median 431.5, SD 115.6 days) in the placebo group.

Efficacy

Primary outcome measure

The stratified log-rank test indicated no significant difference between the two treatments in terms of transition rate (p=0.76). The Kaplan-Meier estimated 6-month transition rates were 5.1% (95%CI 1.3–8.7) in the control group, and 6.7% (95%CI 2.3–10.8) in the omega-3 group. At 12 months, the transition rates were 11.2% (95% CI 5.5–16.7) in the control group and 11.5% (95% CI 5.8–16.9) in the omega-3 group (Figure 2). Cox regression, again stratified for recruitment site and baseline MADRS score, also showed no significant difference between the two groups (hazard ratio 1.1; 95% CI 0.55–2.23; p=0.76).

Secondary outcome measures

General linear model analysis, with an a priori significance threshold of $p<0.05$ and no adjustment for multiple testing, was used to compare the treatments in terms of changes in the symptom and functioning measures between baseline and the 6- and 12-month follow-up visits. Two of these measures showed a trend towards improvement at Month 6: the MADRS (p=0.093) and the SOFAS (p=0.066), while a statistically significant improvement was seen on the global functioning role scale (p=0.017). However, the direction of these changes was in favour of the placebo group. We suggest these are either chance findings, or that for reasons which are not clear, the placebo group may have benefited more from the psychosocial and other treatment interventions. No statistically significant difference was seen between the groups in any of the measures at Month 12 (Table 1). Linear mixed effects modelling was used to compare the two treatments in terms of the rate of improvement over time for each of the symptom and functioning measures. Although there was a significant improvement over time for each measure, the rate of improvement did not significantly differ between the two treatments on any of the measures (Table 1).

Adverse events

Adverse events were assessed at baseline and monthly during the intervention phase, and then at the 6- and 12-month follow-up visits. No statistically significant group differences were observed between the treatment and placebo groups (Supplementary Table 3).

Adherence and concomitant medication

The proportion of adherent participants was 43.1% for the omega-3 group and 41.1% for the placebo group. However, a total of 83 subjects had missing data for the capsule counts (35 from the omega-3 PUFA group, 48 from the placebo group), 9 of whom transitioned to psychosis. In order not to lose subjects from the analysis, these 83 subjects were assumed to be non-adherent. Figure 3 shows the survival curves comparing the two groups for the adherent and non-adherent participants, respectively. As expected, the transition rate was lower in the adherent participants; however, stratified log-rank tests comparing the two treatment groups showed that there was no significant difference between them regardless of adherence status (adherent subjects, p=0.38, non-adherent subjects, p=0.95; Figure 3).

The symptom and functioning measures were further analyzed by taking adherence into account, again using general linear modelling and a linear mixed effects model. Again, no significant difference between the two treatment groups was found (p>0.14 for all measures), irrespective of adherence status.

The mean number of CBCM sessions attended was 11.2 (SD 6.4) for the omega-3 group and 10.3 (6.0) for the placebo group. The overall median number of CBCM sessions attended was 8. Again, stratified log-rank tests showed that there was no significant difference between the treatment groups in terms of transition rate for those with a number of CBCM sessions equal to or below the median (p=0.31), as well as for those above the median (p=0.50).

Concomitant medication use after randomization included antidepressants in 98 (64.1%) of those in the omega-3 group and 91 (60.3%) of those in the placebo group (p=0.57) and anxiolytics in 32 (20.9%) of the participants in the omega-3 group and 44 (29.1%) of those in the placebo group (p=0.13).

Risk class analysis

Risk class analysis was undertaken in an effort to identify participants at highest risk of transition, in order to assess the effectiveness of omega-3 PUFA in this subgroup. Demographic characteristics and symptom and functioning measures were used as potential risk factors and their significance on transition rate was determined using Cox regression analysis in the placebo group to remove any potential intervention effect. The only measures found to be significant were the BPRS total score (p=0.025) and the MADRS total score (0.009). Because these two measures were highly correlated (Pearson correlation 0.67), the MADRS score was chosen as the stratifying factor for this analysis as it had a lower p-value, no missing values, and was

one of the stratifying variables for the randomization. A cut-off score of 14 for MADRS score was found to correspond to the most significant p-value (p=0.001). This score was considered valid as the placebo subjects who had a MADRS total score <14 had an estimated 1-year transition rate of 0%, whereas those with a score ≥14 had an estimated 1-year transition rate of 16.5%. However, when the transition rates of the two treatment groups were compared within the "high-risk" (i.e., those with a MADRS score ≥14) subjects, no significant difference was found (p=0.36) (Figure 4).

Discussion

To our knowledge, this is the first randomized, placebo-controlled multi-centre trial to test the efficacy of long-chain omega-3 PUFAs in preventing transition to psychosis in ultra-high risk young people. Although omega-3 PUFAs were well tolerated, they did not demonstrate an advantage over placebo in the prevention of psychosis at 6- or 12-month follow-up. The two treatment groups also did not differ significantly on secondary outcome measures of psychiatric symptoms and functioning. These findings represent a clear failure to replicate our earlier single-centre trial in 81 participants, in which omega-3 PUFA supplementation showed highly significant and clinically important results, reducing both the risk for progressing to a first episode of psychosis and leading to significant symptomatic and functional improvements,[27] which have now been sustained for a median of 6.7 years.[28]

While one obvious possible explanation for this non-replication is that omega-3 PUFA supplementation is not effective for preventing the onset of psychosis, other explanations may have been responsible. The 12-month transition rate was lower than expected in this trial, and well below that in our previous trial, with an overall proportion of 10.5% (32 of 304 participants). In our previous study, the transition rates were 16.1% at 12 months and 24.7% at 7 years (median) after baseline, respectively. There are two possible explanations for this lower transition rate. Firstly, the manualized CBCM intervention and the high level of antidepressant treatment received by both treatment groups in the current study may have been sufficiently effective to have produced a ceiling effect, beyond which there was no scope for omega-3 PUFA to confer additional benefit. In support of this possibility is the fact that the placebo group in the original trial failed to show the level of symptomatic and functional improvement seen in the current study.[42] Secondly, the sample may have been insufficiently enriched for risk of transition. At first glance the low transition rate might be regarded as having reduced the power of the study to detect an effect; however, there was no trend for efficacy of the omega-3 PUFAs, so more power through a larger sample size would not be likely to address this issue. Rather, the better outcomes, if produced by better treatment or lower risk in the sample, are more appropriately seen as having prevented the main hypothesis from being tested through a ceiling effect. Hence the study is best described as a "failure to replicate" the original findings. It remains possible that omega-3 PUFAs may be beneficial in the absence of other treatments, or possibly in a subsample of cases. Longer term follow up, subgroup analysis and additional studies may clarify these issues.

In relation to these possible interpretations, lower transition rates have been observed over the last decade,[43, 44] and it has been suggested that the increasing awareness of UHR symptoms may have led to a more rapid referral of young people, resulting in a reduced duration of untreated symptoms.[45, 46] However, this does not seem to have been the case in the current study, and furthermore the level of baseline symptoms and functioning is similar to those in earlier studies, including the original omega-3 trial. The decline in transition rates could also indicate that psychosocial treatment is more effective in these earlier stages of illness, an important point for the design of future studies. Many trials have shown that CBT is effective in delaying and reducing transition, [15] and in contrast to our original study, all patients in the present study received substantial levels of a high-quality CBT-based intervention. In addition, the high proportion of participants who received antidepressant medication (62% compared to 10% in the original study) may also have contributed to the low overall transition rate. Previous studies have suggested, but not demonstrated, an effect of antidepressant medication in decreasing transition rate in UHR samples.[33-36] In this study, antidepressant medication was prescribed to those participants who were more symptomatic and depressed, and who therefore were at higher risk of transition to psychosis, thus potentially having a selectively greater effect on reducing the overall transition rate. Given the still low, but rising, 12-month transition rate observed in the present study, a longer-term follow-up in this cohort is warranted, and a 24-month follow-up is currently being completed. It is possible, based on the long-term efficacy of omega-3 in the original sample that a differential trajectory could appear later in the omega-3 group; however, in the earlier trial there was an early, as well as a sustained, effect. It is possible that in the current study the early effect was masked by the potency of the other treatments.

Adherence was modest in this study: 41.1% in the placebo group and 43.1% in the fish oil group. In comparison, the mean rate of adherence to study medication in the Vienna omega-3 study was 81.4% in the omega-3 group and 75.4% in the placebo group.[27] This comparatively lower adherence may have made it even more difficult to detect statistically significant differences in the secondary outcome measures.

Strengths of the study include the randomized, placebo-controlled design, the use of standardized inclusion and exit criteria, inter-rater reliability testing, the monitoring of treatment adherence, and the confirmation at 12-month follow-up by means of SCID and case review that all people who met the exit criteria had made transitions to genuine psychotic disorders.

A limitation of this study is that the use of non-study omega-3 PUFA supplements cannot be excluded. In pharmaceutical trials, the control group is not exposed to the study drug. In contrast, in omega-3 PUFA trials, the test agent may be present in both the experimental and control groups,[47] because the non-study intake of omega-3 PUFAs cannot be prevented. It is thus possible that non-study omega-3 intake may have decreased the difference in omega-3 status between the treatment groups. As demonstrated by cell membrane fatty acid data, there was no substantive non-study fish oil supplement intake in our earlier trial. However, it is possible that non-study fish oil supplementation or increased fish intake may have

occurred in the present trial, as both the awareness of the potential health benefits of omega-3 PUFAs and the availability of fish oil supplements has sharply increased over the last decade.

It is also possible that omega-3 PUFAs may have stronger effects in subgroups characterized by certain biological or phenotypic factors (i.e., fatty acid profiles, inflammatory markers, oxidative stress markers and/or higher levels of negative symptoms[28]), and thus can be considered as moderators of the clinical response in these individuals [48]. In this regard, it has recently been shown that omega-3 PUFAs are specifically effective in people with high levels of inflammation.[49] In a next step, subgroup analyses using information on baseline membrane fatty acid levels and inflammatory markers will be carried out to address this question. We are also investigating whether biological measures of omega-3 PUFA intake that accurately define adherence to study medication as well as non-study intake (i.e., independent of group allocation), such as changes in erythrocyte membrane fatty acid levels, will provide a clearer view of whether omega-3 PUFAs were beneficial in subgroups of this cohort. However, irrespective of the outcomes of these analyses, it is already clear that when used in addition to high quality biopsychosocial treatment, the benefits of omega-3 PUFAs appear to be more modest than originally thought.

In summary, this trial has failed to replicate the findings of our previous study.[27] No other multi-centre clinical trials have so far been completed that have examined the effect of omega-3 PUFAs in the prevention of psychosis, although some are currently underway. These, ongoing analysis of the data from the current study, and future research, will help to ultimately determine whether omega-3 PUFAs have a role in the reduction of risk and early treatment of psychotic disorder.

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References

1. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull.* 1996;22(2):283-303.

2. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr Bull.* 1996;22(2):353-370.

3. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophr Res.* 2003;60(1):21-32.

4. Fusar-Poli P, Rocchetti M, Sardella A, Avila A, Brandizzi M, Caverzasi E, Politi P, Ruhrmann S, McGuire P. Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *Br J Psychiatry.* 2015;207(3):198-206.

5. Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res.* 2004;67(2-3):131-142.

6. Yung AR, McGorry PD. The initial prodrome in psychosis: descriptive and qualitative aspects. *Aust N Z J Psychiatry.* 1996;30(5):587-599.

7. McGorry PD, Yung AR, Phillips LJ. The "close-in" or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. *Schizophr Bull.* 2003;29(4):771-790.

8. Addington J, Cadenhead KS, Cannon TD, Cornblatt B, McGlashan TH, Perkins DO, Seidman LJ, Tsuang M, Walker EF, Woods SW, Heinssen R. North American Prodrome Longitudinal Study: a collaborative multisite approach to prodromal schizophrenia research. *Schizophr Bull.* 2007;33(3):665-672.

9. Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, Heinssen R. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry.* 2008;65(1):28-37.

10. Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophr Bull.* 2009;35(5):894-908.

11. Klosterkotter J, Ruhrmann S, Schultze-Lutter F, Salokangas RK, Linszen D, Birchwood M, Juckel G, Morrison A, Vazquez-Barquero JL, Hambrecht M, H VONR. The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. *World Psychiatry.* 2005;4(3):161-167.

12. Ruhrmann S, Schultze-Lutter F, Salokangas RK, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, von Reventlow HG, Klosterkotter J. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Arch Gen Psychiatry.* 2010;67(3):241-251.

13. Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rossler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ, Valmaggia L, Cannon T, Velthorst E, De Haan L, Cornblatt B, Bonoldi I, Birchwood M, McGlashan T, Carpenter W, McGorry P, Klosterkotter J, McGuire P, Yung A. The Psychosis High-Risk State: A Comprehensive State-of-the-Art Review. *JAMA Psychiatry.* 2013;70(1):107-120.

14. Berger GE, Wood SJ, Ross M, Hamer CA, Wellard RM, Pell G, Phillips L, Nelson B, Amminger GP, Yung AR, Jackson G, Velakoulis D, Pantelis C, Manji H, McGorry PD. Neuroprotective effects of low-dose lithium in individuals at ultra-high risk for psychosis. A longitudinal MRI/MRS study. *Curr Pharm Des.* 2012;18(4):570-575.

15. van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, McGorry P, Cuijpers P. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. *Schizophr Res.* 2013;149(1-3):56-62.

16. McGorry P, Nelson B. Why We Need a Transdiagnostic Staging Approach to Emerging Psychopathology, Early Diagnosis, and Treatment. *JAMA Psychiatry.* 2016:1-2.

17. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry.* 2006;40(8):616-622.

18. McGorry PD. Risk syndromes, clinical staging and DSM V: new diagnostic infrastructure for early intervention in psychiatry. *Schizophr Res.* 2010;120(1-3):49-53.

19. McGorry PD. The next stage for diagnosis: validity through utility. *World Psychiatry.* 2013;12(3):213-215.

20. McGorry PD. Early clinical phenotypes, clinical staging, and strategic biomarker research: building blocks for personalized psychiatry. *Biol Psychiatry.* 2013;74(6):394-395.

21. Addington J, Epstein I, Liu L, French P, Boydell KM, Zipursky RB. A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. *Schizophr Res.* 2011;125(1):54-61.

22. Morrison AP, French P, Walford L, Lewis SW, Kilcommons A, Green J, Parker S, Bentall RP. Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. *Br J Psychiatry.* 2004;185:291-297.

23. Morrison AP, French P, Parker S, Roberts M, Stevens H, Bentall RP, Lewis SW. Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. *Schizophr Bull.* 2007;33(3):682-687.

24. Morrison AP, French P, Stewart SL, Birchwood M, Fowler D, Gumley AI, Jones PB, Bentall RP, Lewis SW, Murray GK, Patterson P, Brunet K, Conroy J, Parker S, Reilly T, Byrne R, Davies LM, Dunn G. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *Bmj.* 2012;344:e2233.

25. van der Gaag M, Nieman DH, Rietdijk J, Dragt S, Ising HK, Klaassen RM, Koeter M, Cuijpers P, Wunderink L, Linszen DH. Cognitive behavioral therapy for subjects at ultrahigh risk for developing psychosis: a randomized controlled clinical trial. *Schizophr Bull.* 2012;38(6):1180-1188.

26. Ising HK, Kraan TC, Rietdijk J, Dragt S, Klaassen RM, Boonstra N, Nieman DH, Willebrands-Mendrik M, van den Berg DP, Linszen DH, Wunderink L, Veling W, Smit F, van der Gaag M. Four-Year Follow-up of Cognitive Behavioral Therapy in Persons at Ultra-High Risk for Developing Psychosis: The Dutch Early Detection Intervention Evaluation (EDIE-NL) Trial. *Schizophr Bull.* 2016.

27. Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, McGorry PD, Berger GE. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry.* 2010;67(2):146-154.

28. Amminger GP, Schafer MR, Schlogelhofer M, Klier CM, McGorry PD. Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. *Nat Commun.* 2015;6:7934.

29. Authority TG. *Note for guidance on Good Clinical Practice: Annotated with TGA comments (CPMP/ICH/135/95).* Canberra: Therapeutic Goods Authority; 2000.

30. Markulev C, McGorry PD, Nelson B, Yuen HP, Schaefer M, Yung AR, Thompson A, Berger G, Mossaheb N, Schlogelhofer M, Smesny S, de Haan L, Riecher-Rossler A, Nordentoft M, Chen EY, Verma S, Hickie I, Amminger GP. NEURAPRO-E study protocol: a multicentre randomized controlled trial of omega-3 fatty acids and cognitive-behavioural case management for patients at ultra high risk of schizophrenia and other psychotic disorders. *Early Interv Psychiatry.* 2015.

31. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K, Buckby J. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry.* 2005;39(11-12):964-971.

32. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.

33. McGorry PD, Nelson B, Amminger GP, Bechdolf A, Francey SM, Berger G, Riecher-Rossler A, Klosterkotter J, Ruhrmann S, Schultze-Lutter F, Nordentoft M, Hickie I, McGuire P, Berk M, Chen EY, Keshavan MS, Yung AR. Intervention in individuals at ultra high risk for psychosis: a review and future directions. *J Clin Psychiatry.* 2009;70(9):1206-1212.

34. McGorry PD, Nelson B, Goldstone S. Providing care to young people with emerging risk of psychosis: Balancing potential risks and benefits. *Clinical Practice.* 2012;9(6):669-682.

35. Cornblatt BA, Lencz T, Smith CW, Olsen R, Auther AM, Nakayama E, Lesser ML, Tai JY, Shah MR, Foley CA, Kane JM, Correll CU. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. *J Clin Psychiatry.* 2007;68(4):546-557.

36. Fusar-Poli P, Frascarelli M, Valmaggia L, Byrne M, Stahl D, Rocchetti M, Codjoe L, Weinberg L, Tognin S, Xenaki L, McGuire P. Antidepressant, antipsychotic and psychological interventions in subjects at high clinical risk for psychosis: OASIS 6-year naturalistic study. *Psychol Med.* 2015;45(6):1327-1339.

37. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep.* 1962;10:799-812.

38. Andreasen NC. *Scale for the assessment of negative symptoms (SANS).* Iowa City: University of Iowa; 1983.

39. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;133:429-435.

40. Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. *Am J Psychiatry.* 1992;149(9):1148-1156.

41. Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CE, Cannon TD. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophr Bull.* 2007;33(3):688-702.

42. Mossaheb N, Schafer MR, Schlogelhofer M, Klier CM, Cotton SM, McGorry PD, Amminger GP. Effect of omega-3 fatty acids for indicated prevention of young patients at risk for psychosis: when do they begin to be effective? *Schizophr Res.* 2013;148(1-3):163-167.

43. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Barale F, Caverzasi E, McGuire P. Predicting psychosis: a meta-analysis of evidence. *Arch Gen Psychiatry.* 2012;69(3):220-229.

44. Simon AE, Velthorst E, Nieman DH, Linszen D, Umbricht D, de Haan L. Ultra high-risk state for psychosis and non-transition: a systematic review. *Schizophr Res.* 2011;132(1):8-17.

45. Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, Phillips L, McGorry P. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophr Bull.* 2007;33(3):673-681.

46. Wiltink S, Velthorst E, Nelson B, McGorry PM, Yung AR. Declining transition rates to psychosis: the contribution of potential changes in referral pathways to an ultra-high-risk service. *Early Interv Psychiatry.* 2015;9(3):200-206.

47. James MJ, Sullivan TR, Metcalf RG, Cleland LG. Pitfalls in the use of randomised controlled trials for fish oil studies with cardiac patients. *Br J Nutr.* 2014;112(5):812-820.

48. Kraemer HC. Messages for Clinicians: Moderators and Mediators of Treatment Outcome in Randomized Clinical Trials. *Am J Psychiatry.* 2016;173(7):672-679.

49. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoos A, Walker R, Mischoulon D. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. *Mol Psychiatry.* 2016;21(1):71-79.

Figure Legends

Figure 1: CONSORT diagram of participant distribution.

Figure 2: Survival curves of the rate of transition to psychosis in the omega-3 and placebo groups.

Figure 3: Survival curves for the rate of transition in the two groups, based on adherence status.

Figure 4: Survival curves for the rate of transition in high-risk subjects (those with a baseline MADRS score ≥ 14).

Table 1: General linear model analysis comparing the placebo and omega-3 groups in terms of change between baseline and follow-up (Months 6 and 12), and linear mixed model analysis comparing the two treatments in terms of rate of change over time.

General linear model analysis								Linear mixed effects model analysis			
		Month 6 minus baseline			Month 12 minus baseline			p-value[2]	Overall estimated rate of change	Standard error	p-value[3]
		Mean	SD	p-value[1]	Mean	SD	p-value[1]				
BPRS total	Placebo	-7.4	8.5	0.364	-7.8	8.4	0.999	0.477	-0.018	0.0015	<0.001
	Fish oil	-7.3	8.5		-7.8	9.3					
BPRS psychotic subscale	Placebo	-2.4	3.2	0.850	-2.5	3.3	0.656	0.912	-0.006	0.0005	<0.001
	Fish oil	-2.3	2.5		-2.3	3.1					
SANS total	Placebo	-6.5	11.7	0.139	-6.2	11.7	0.894	0.825	-0.018	0.0020	<0.001
	Fish oil	-5.9	9.6		-7.5	11.7					
SANS affective flattening or blunting	Placebo	-1.8	4.6	0.237	-1.4	4.8	0.894	0.491	-0.005	0.0008	<0.001
	Fish oil	-1.9	4.0		-2.2	4.8					
SANS alogia	Placebo	-0.8	2.6	0.137	-0.6	2.4	0.596	0.618	-0.002	0.0004	<0.001
	Fish oil	-0.8	2.4		-1.1	2.5					
SANS avolition–apathy	Placebo	-1.4	3.0	0.448	-1.5	3.4	0.725	0.598	-0.004	0.0005	<0.001
	Fish oil	-1.3	2.8		-1.7	2.9					
SANS anhedonia–asociality	Placebo	-2.1	4.0	0.397	-2.3	4.3	0.801	0.587	-0.005	0.0007	<0.001
	Fish oil	-1.7	3.5		-2.0	4.3					
SANS attention	Placebo	-0.4	1.4	0.224	-0.3	1.5	0.205	0.925	-0.001	0.0003	<0.001
	Fish oil	-0.3	1.8		-0.7	1.8					
YMRS total	Placebo	-1.1	3.0	0.244	-0.9	2.6	0.612	0.696	-0.002	0.0005	<0.001
	Fish oil	-0.9	3.1		-0.8	3.1					
MADRS total	Placebo	-9.3	8.4	0.093	-9.0	-9.6	0.717	0.788	-0.020	0.0016	<0.001
	Fish oil	-7.9	8.7		-9.6	-9.4					
SOFAS	Placebo	12.6	14.9	0.066	14.3	16.8	0.949	0.362	0.036	0.0030	<0.001
	Fish oil	8.9	16.5		14.7	19.1					
Global functioning: social	Placebo	0.6	1.4	0.452	0.7	1.6	0.471	0.406	0.002	0.0003	<0.001
	Fish oil	0.5	1.2		0.5	1.4					
Global functioning: role	Placebo	0.9	1.6	0.017	1.0	2.0	0.782	0.634	0.002	0.003	<0.001
	Fish oil	0.5	1.7		0.9	1.7					

[1] P-value for comparing placebo and omega-3 groups in terms of change between follow-up (Month 6 or 12) and baseline.

[2] P-value for comparing placebo and omega-3 groups in terms of rate of improvement over time from baseline to Month 12.

[3] P-value for the overall estimated rate of change.

Supplementary Table 1: Baseline demographic data for the study cohort

		Placebo	**Fish oil**
Age, years		18.9±4.3	19.4±4.8
Gender (% subjects)	Female	59.6	49.0
Race (% subjects)	Caucasian	80.1	80.4
	Black or African American	2.6	2.0
	Asian	10.6	13.1
	Other	3.3	3.3
	Missing	3.3	1.3
Highest level of education (% subjects)	Primary school	37.1	35.9
	Secondary school, discontinued	17.9	17.6
	Secondary school, completed	27.8	28.8
	Trade or technical training	9.9	10.5
	Undergraduate university course	3.3	5.9
	Missing	4.0	1.3

Supplementary Table 2: Baseline symptomatology in the study cohort

Symptom measure		**Mean**	**SD**
BPRS	Placebo	40.7	8.9
	Fish oil	41.9	10.6
SANS	Placebo	17.4	12.9
	Fish oil	19.2	13.4
YMRS	Placebo	3.0	2.9
	Fish oil	3.3	3.1
MADRS	Placebo	19.1	9.2
	Fish oil	19.4	8.9
SOFAS	Placebo	53.5	12.2
	Fish oil	53.2	11.8
Global functioning (social)	Placebo	6.5	1.3
	Fish oil	6.5	1.2
Global functioning (role)	Placebo	5.9	1.5
	Fish oil	6.0	1.5

Supplementary Table 3: Adverse events

Event category	Placebo (% subjects)	Fish oil (% subjects)	p-value*
Autonomous nervous system	7.9	12.4	0.272
Extrapyramidal	3.3	8.5	0.094
Gastrointestinal	27.2	34.6	0.198
Hormonal	8.6	5.2	0.349
Increased bleeding	0.7	0	0.995
Neurological	5.3	9.8	0.205
Psychological	9.9	13.1	0.498
Sexual	0.7	4.6	0.076
Skin	4.6	3.3	0.751
Sleep-related	16.6	13.7	0.597
Other	14.6	16.3	0.789

* The p-value of the Chi-square test.