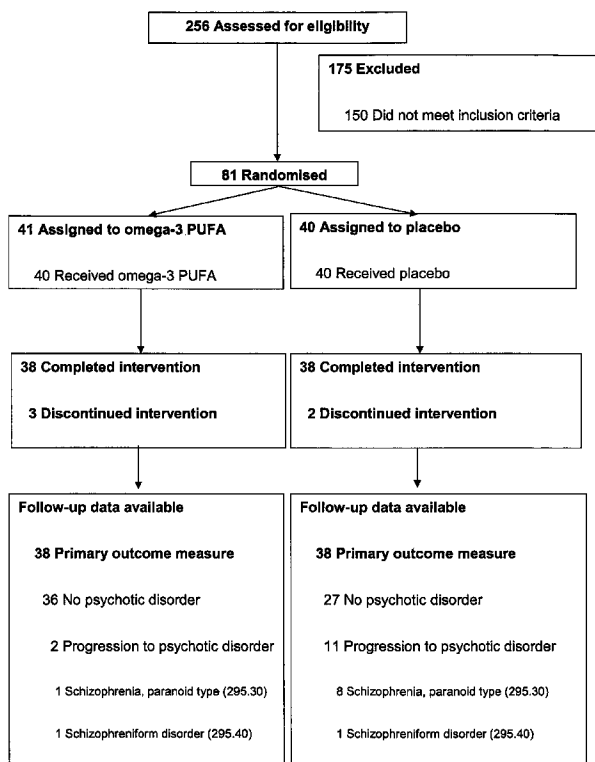




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 (72) Inventeurs/Inventors:
AMMINGER, GUNTER PAUL, AT;
MCGORRY, PATRICK DENNISTOUN, AU
 (73) Propriétaire/Owner:
ORYGEN YOUTH HEALTH RESEARCH CENTRE, AU
 (74) Agent: AIRD & MCBURNEY LP

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 (54) Title: PREVENTION OF PSYCHOTIC DISORDERS AND/OR TREATMENT OF PSYCHOTIC SYMPTOMS



(57) **Abrégé/Abstract:**

The present invention relates to methods of preventing a psychotic disorder in a subject in need of intervention including administering to the subject a composition including EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid). Methods of treating pre-psychotic symptoms in a subject, including administering to the subject a composition including EPA and DHA are also included.

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- (71) **Applicant (for all designated States except US):** ORY-GEN RESEARCH CENTRE [AU/AU]; 35 Poplar Road, Parkville, VIC 3052 (AU).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** AMMINGER, Gunter, Paul [AT/AT]; Porzellangasse 60/5/41-43, A-1090 Vienna (AT). MCGORRY, Patrick, Dennistoun [AU/AU]; c/- 35 Poplar Road, Parkville, VIC 3052 (AU).
- (74) **Agent:** FREEHILLS PATENT & TRADE MARK ATTORNEYS; Level 43, 101 Collins Street, Melbourne, VIC 3000 (AU).

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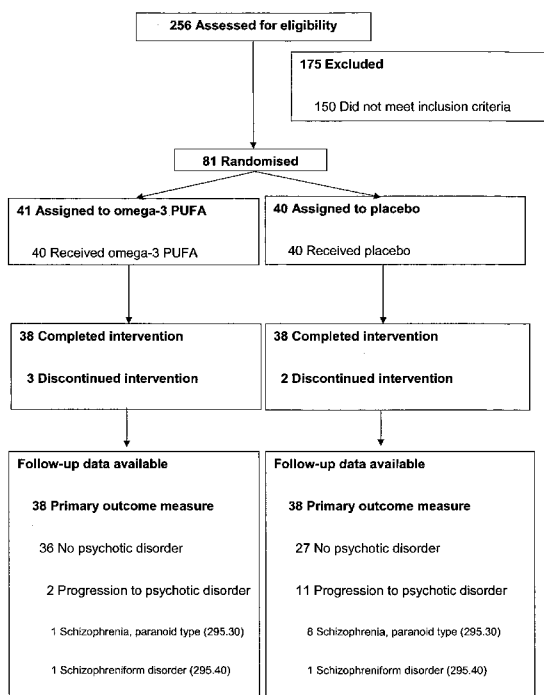
(54) **Title:** PREVENTION OF PSYCHOTIC DISORDERS AND/OR TREATMENT OF PSYCHOTIC SYMPTOMS

Figure 2

(57) **Abstract:** The present invention relates to methods of preventing a psychotic disorder in a subject in need of intervention including administering to the subject a composition including EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid). Methods of treating pre-psychotic symptoms in a subject, including administering to the subject a composition including EPA and DHA are also included.

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Prevention of psychotic disorders and/or treatment of psychotic symptoms

Field of the invention

The invention is directed toward methods of prevention of psychotic disorders, including
5 schizophrenia, in particular, inhibiting such disorders from developing.

Background of the invention

Psychotic disorders are a group of serious mental illnesses with an average age of onset in late adolescence or early adulthood. The most common psychotic disorders include schizophrenia, bipolar disorder with psychotic features, major depression with
10 psychotic features. Psychotic disorders are primarily characterized by the presence of hallucinations, delusions (such as hearing voices and paranoia) and related changes in behaviour.

Schizophrenia represents the majority of psychotic disorders (about 60%). In 1990, Schizophrenia was estimated to be the 10th leading cause of non-fatal burden in the
15 world, accounting for 2.6% of total "years of life lived with disability" (YLD), around the same percentage as congenital malformations. The Global Burden of Disease 2000 study found the disease to be the 7th leading cause of YLDs at the global level, accounting for 2.8% of total global YLD.

Whilst the potential benefit of preventing psychotic disorders is great, currently available
20 strategies for prevention by treating attenuated symptoms with pharmacological psychiatric interventions (e.g., antipsychotics, antidepressants, mood stabilizers) are not ideal.

Previous trials have investigated the preventive use of antipsychotic medications in ultra-high-risk groups. One study for example showed that a combination of risperidone
25 and cognitive therapy for 6 months was significantly more effective than supportive counselling at end of intervention, but not at 12-month follow-up. A second study,

compared 12 months intervention with olanzapine to placebo and found no significant intervention group differences. It was concluded that the benefits of pre-onset intervention with antipsychotics may outweigh the risks to a degree sufficient to endorse future trials. However, the use of antipsychotic medication for indicated prevention
5 remains controversial even in research settings because of the high number of false positives (about 70-80% of people who meet ultra-high-risk criteria do not progress to psychotic disorder within one year). Stigmatization associated with the use of antipsychotics, and unwanted side effects which include metabolic changes, sexual dysfunction and weight gain are often not acceptable. Other side effects may include
10 dyslipidaemia, cardiac arrhythmia and osteoporosis.

The use of such medication as a preventative therapy is controversial because there is no certainty that patients at risk of developing the psychosis will go on to develop the disease. Many patients fail to respond to these medications or only to a limited degree. None of these available medicines reliably produce a complete remission of symptoms.

15 The diagnostic criteria used to identify individuals at risk for psychotic disorders is imprecise, particularly given that not all individuals assessed at high risk will transition to a psychotic disorder within one year. The transition rate for individuals may vary between 5%-40% depending on the population which the risk is assessed against. Therefore pharmacological interventions are not ideal since not all individuals may
20 benefit in the long term and would also lead to unnecessary costs and waste of resources.

In order to lower the risk of individuals transitioning to psychosis or a psychotic disorder, intervention therapies are needed. There is also a need for intervention therapies that reduce or minimise biological or psychosocial damage that manifests during the onset
25 of psychotic disorders. There is also a need for preventative therapies with minimal risk of unwanted side-effects and also with a sustained therapeutic effect.

In contrast, omega-3 polyunsaturated fatty acids (PUFA) have been shown to be very safe even when used in relatively high doses and except from gastrointestinal symptoms like fishy eructation, nausea and loose stools which may occur, they are free

of clinically relevant side effects. They have the advantage of excellent tolerability, public acceptance, relatively low costs, and benefits for general health.

Some therapeutic effects of omega-3 PUFA on cardiovascular diseases are already well known. It has also been suggested that these PUFAs are essential for normal pre-natal
5 or post-natal development of retina and the brain.

US 6,384,077 (Peet *et al*) describes a method of treating schizophrenia and related disorders in patients diagnosed as already having the disorder by administration of highly purified eicosapentanoic acid (EPA) in combination with a drug that acts primarily on neurotransmitter metabolism of receptors. The composition used in this method
10 contains at least 90% or more EPA, and less than 5% docosahexaenoic acid (DHA).

US 2007/0161705 (Bruzzeze) describes use of omega-3 PUFA, including a mixture of DHA and EPA for prevention and/or treatment of disturbances of the central nervous system including schizophrenia.

Although it is known to a certain degree that compositions comprising combinations of
15 omega-3 PUFA may have shown effectiveness in the treatment of mental disorders, none of the literature provide a reasonable expectation that the use of such omega-3 fatty acids may prevent or delay the onset of such diseases in individuals assessed at ultra high risk of developing a psychotic disorder. Moreover, there is no published evidence that such treatment could have long term benefits for certain individuals, after
20 the treatment or intervention has ceased.

The present invention seeks to at least minimise one of the above limitations and/or address these needs.

Summary of the invention

In one aspect, there is provided a method of preventing a psychotic disorder in a subject
25 in need of intervention including administering to the subject a composition including EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid).

In another aspect, the present invention also provides a method of preventing a psychotic disorder in a subject including the steps of:

assessing the subject for risk of developing a psychotic disorder;

5 selecting subjects that meet the Ultra High Risk (UHR) criteria for developing a psychotic disorder; and

administering to the selected subject a composition including EPA and DHA.

In a further aspect, the invention provides a method of treating pre-psychotic symptoms in a subject, including administering to the subject a composition including EPA and DHA.

10 Preferably the composition is administered for a defined period, preferably for at least about 3 months up to about 6 months.

In another aspect, the present invention provides use of a composition including EPA and DHA for the preparation of a medicament for preventing a psychotic disorder in a subject in need of intervention.

15 In a further aspect the present invention provides use of a composition including EPA and DHA for the preparation of a medicament for treating pre-psychotic symptoms in a subject.

In yet a further aspect, the present invention provides a composition including EPA and DHA when used for the prevention of a psychotic disorder in a subject in need of
20 intervention.

In another aspect, the present invention provides a composition including EPA and DHA when used for the treatment of pre-psychotic symptoms in a subject.

In yet a further aspect, there is provided a kit for preventing a psychotic disorder including a composition including EPA and DHA and instructions for use of the kit.

In another aspect, the present invention provides a kit for treating pre-psychotic symptoms including a composition including EPA and DHA and instructions for use of the kit.

In accordance with an aspect, there is provided a use of EPA(eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for treating pre-psychotic symptoms in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the medicament in a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids in the medicament, the medicament is for administration once per day, wherein the medicament is for administration to the subject for at least 12 weeks, and wherein the subject's risk of transition to psychosis is reduced for at least 9 months after treatment is ceased.

In accordance with an aspect, there is provided a use of EPA(eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for intervening treatment in a subject of between about 13 and about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the medicament in a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids, the medicament is for administration once per day, wherein the medicament is for administration to the subject for at least 12 weeks, wherein the intervening treatment reduces the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder, and wherein the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder is reduced for at least 9 months after the intervening treatment is ceased.

In accordance with an aspect, there is provided a use of EPA(eicosapentanoic acid) and DHA (docosahexaenoic acid) in a unit dosage form for treating pre-psychotic symptoms in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic

disorder, wherein the EPA and DHA are present in the unit dosage form a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids in the unit dosage form for administration once per day, wherein the unit dosage form is for administration to the subject for at least 12 weeks, and wherein the subject's risk of transition to psychosis is reduced for at least 9 months after treatment is ceased.

In accordance with an aspect, there is provided a use of EPA(eicosapentanoic acid) and DHA (docosahexaenoic acid) in a unit dosage form for intervening treatment in a subject of between about 13 and about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the unit dosage form in a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids and the unit dosage form is for administration once per day, wherein the unit dosage form is for administration to the subject for at least 12 weeks, and wherein the intervening treatment reduces the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder.

In accordance with an aspect, there is provided a use of EPA(eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for treating pre-psychotic symptoms in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the medicament is for administration to the subject for a period of 6 months to arrest the development of pre-psychotic symptoms for at least 12 months after beginning treatment.

In accordance with an aspect, there is provided a use of EPA(eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for intervening treatment in a subject of between about 13 and about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a

psychotic disorder, wherein the medicament is for administration to the subject for a period of 6 months to reduce the risk that the subject will transition to psychosis during the 12 months following commencing the administration.

In accordance with an aspect, there is provided a method of verifying that a subject, having previously been administered a composition comprising EPA and DHA for an intervention period of 6 months, is at a reduced risk of transitioning to psychosis, wherein the subject meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, comprising: assessing the subject for transition to psychosis after 12 months from commencing the administration, so as to verify the reduced risk that a subject will transition to psychosis..

In accordance with a further aspect, there is provided use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for increasing the functioning in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the medicament in a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids in the medicament, the medicament is for administration once per day to the subject, wherein the medicament is for administration to the subject for at least 12 weeks, wherein the increase in functioning of the subject is assessable, and wherein the subject's functioning remains increased at least 9 months after said use is ceased.

In accordance with a further aspect, there is provided use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in a unit dosage form for increasing the functioning in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the unit dosage form a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids in the unit dosage form for administration once per day, wherein the unit dosage form is for

administration to the subject for at least 12 weeks, and wherein the subject's functioning remains increased for at least 9 months after said use is ceased.

In accordance with a further aspect, there is provided use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for increasing the functioning in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the medicament is for administration to the subject for a period of 6 months to increase the functioning of the subject for at least 12 months after beginning said use.

Brief description of the figures

Figure 1 Pie graphs showing fatty acid component of (A) active capsules and (B) placebo capsules used in the study of the example.

Figure 2 Flow diagram showing enrolment, selection and outcomes of the study of the example.

Figure 3 Kaplan-Meier survival analysis of transition from prodromal state to psychosis in patients assigned to omega-3 fatty acids (n=41) or placebo (n=40) in the study of the example.

Figure 4 shows mean scores (95% CI) for secondary outcome measures for omega-3 fatty acids (square) and placebo (circle). Points represent means, and bars represent the 95%CI. For the PANSS the minimum total score is 30, and the minimum score for the positive, negative, and global subscale is 7, 7, and, 16, respectively. The MADRS measures the severity of 10 symptoms on a scale from 0 to 6. The GAF measures social, occupational and psychological functioning on a single numeric scale (0 through 100), with higher scores indicating better functioning.

Detailed description

The inventor(s) have found that following administration of a composition including eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) over a defined period in ultra high risk (UHR) individuals, the conversion rate to psychosis for those individuals receiving the composition was significantly lower than those individuals receiving a placebo at the end of this period.

Unexpectedly, when the same group of individuals were followed up at intervals after the end of intervention, the rate of conversion to psychosis was still significantly lower in the group that received the omega-3 fatty acid composition compared to the placebo group. Thus a sustained effect from the intervention was observed in the group of UHR
5 individuals who received polyunsaturated fatty acids (PUFA) compared to placebo beyond the period of intervention. Furthermore, the individuals who received the omega-3 fatty acid composition showed significantly reduced symptoms and improved functioning, beyond the intervention period, which was again unexpected.

The finding that the risk of individuals developing a psychotic disorder may be
10 significantly reduced in those individuals assessed to be at ultra high risk of developing a psychotic disorder is significant. This finding therefore provides a potential for a positive outcome for those individuals without the stigma and associated side-effects with available medications.

The most striking finding by the inventors is that group differences were sustained after
15 cessation of the intervention. Trials of antipsychotics have not found this. Without being bound by any theory or mode of action, the sustained effect may be explained by neuroprotective properties as omega-3 PUFA can induce antiapoptotic and antioxidative factors. In support of this, in vivo ¹H-MRS has demonstrated that EPA can increase glutathione in temporal lobes of first-episode psychosis patients, which may protect
20 neurons from oxidative stress.

In one aspect of the invention there is provided a method of preventing a psychotic disorder in a subject in need of intervention including administering to the subject a composition including EPA and DHA.

Psychotic disorders are primarily characterized by the presence of hallucinations,
25 delusions (such as hearing voices and paranoia) and related changes in behaviour. These disorders are comprised of a group of serious illnesses of unknown aetiology, with an average age of onset in late adolescence or early adulthood, and a lifetime prevalence of 3-5%. Schizophrenia, schizoaffective disorder or schizotypal disorders represent the largest group of psychotic disorders (about 60%). Other forms of

psychotic disorders include for example affective psychosis, bipolar disorder with psychotic features, major depression with psychotic features.

Schizophrenia is a severe mental disorder which usually starts in adolescence or early adult life and often has a chronic disabling course. It is generally characterized by
5 fundamental and characteristic distortions in form and content of thinking and perception (loosening of associations, delusions, and hallucinations), mood (flattened, inappropriate, or blunted affect) and behaviour (bizarre, apparently purposeless and stereotyped activity or inactivity).

Psychotic disorders, in particular schizophrenia, may be caused by a combination of
10 genetic or biological predisposition as well as other factors such as prepregnancy factors, pregnancy stress, other prenatal factors, social stress, family stress or environmental stressors during a person's life. Schizophrenia has also been associated with a chemical imbalance in the brain, involving dysregulation of the dopaminergic and serotonergic neurotransmitter systems.

15 In this invention, the subject in need of intervention is an individual diagnosed or assessed to be at "Ultra High Risk" (UHR) of developing or transitioning to a psychotic disorder, in particular, a psychotic disorder within 12 months from commencement of treatment.

Assessment of individuals to be at "ultra-high-risk" (UHR) of developing or transitioning
20 to a psychotic disorder uses a combination of trait and state risk factors. The UHR criteria identify individuals with attenuated psychotic symptoms with a risk of developing psychosis within 12 months of the assessment.

Assessment may be determined using international diagnostic criteria (such as those contained in the DSM IV or the ICD 10) to interpret the results of structured or
25 unstructured interviews (e.g. Structured Clinical Interview SCID for DSM IV). These criteria are used to distinguish between subthreshold and full threshold psychotic disorders. DSM IV classification system is otherwise known as the Diagnostic and

Statistical Manual of Mental Disorders (DSM) is a widely used handbook amongst mental health professionals for diagnosing and categorising mental disorders.

UHR individuals may be assessed as having met criteria for one or more of the following three defined groups for risk factors for psychosis (also summarised in Table 1 below):

- (1) attenuated positive psychotic symptoms;
- (2) transient psychosis; and
- (3) genetic risk plus decrease in functioning.

These individuals are also referred to as showing pre-psychotic symptoms.

10 The symptoms of psychotic disorders are diverse, encompassing almost every aspect of cognition and behaviour and may be characterized as positive or negative symptoms. Positive symptoms are those that are brought on by the disorder (e.g. hallucinations, delusions). Negative symptoms are those qualities taken away by the illness (e.g. one's drive and motivation are gone). These symptoms may be scored according to the

15 Positive and Negative Syndrome Scale (PANSS). PANSS is a medical scale used for measuring symptom severity of patients with schizophrenia. It is widely used in the study of antipsychotic therapy. The name refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association: positive symptoms, which refer to an excess or distortion of normal functions, and negative symptoms,

20 which represent a diminution or loss of normal functions.

The PANSS contains 30 symptoms (7 positive, 7 negative and 16 global) which are rated on scale 0=absent to 6=extreme).

The individuals assessed as being at UHR are preferably young. Young individuals are

25 considered to be between the ages of about 13 and about 25 years of age.

In this specification, prevention or preventing or grammatical variations of this term means arresting the development of symptoms in individuals assessed to be at UHR for developing a psychotic disorder. In this specification, the terms inhibition and prevention may be used interchangeably. Intervention or intervening in this instance, is for the purpose of inhibiting a psychotic disorder from occurring by reducing the severity of a psychotic disorder subthreshold manifestation of psychosis.

Prevention is considered to be successful if first episode psychosis (FEP) has not occurred for an extended period following the intervention period, preferably 1 year (or about 12 months) following the beginning of the intervention period.

The composition is administered to a subject in need of intervention for a limited period. Preferably the period of administration is between about 3 months up to about 6 months. Most preferably, the administration is for about 3 months. This period is referred to as the "intervention period". Although the intervention period (or period of administration) is for a defined period, it is also contemplated that these patients may continue administration of the composition beyond the intervention period. This may be continued indefinitely.

Once the intervention period has ceased, the individual may be continually monitored for any progression or regression of symptoms.

In another aspect, the present invention also provides a method of preventing a psychotic disorder in a subject including the steps of:

assessing the subject for risk of developing a psychotic disorder;

selecting subjects that meet the Ultra High Risk (UHR) criteria for developing a psychotic disorder; and

administering to the selected subject a composition including EPA and DHA.

In yet a further aspect, the present invention provides use of a composition including EPA and DHA for the preparation of a medicament for preventing a psychotic disorder in a subject in need of intervention.

Young individuals diagnosed with attenuated psychotic symptoms at UHR for psychosis
5 have shown structural brain abnormalities prior to their first episode psychosis (FEP),
that further progress during transition to full threshold psychotic disorder, suggesting
that active biological processes are involved even at this early stage of progression of
the disorder. Accordingly, without being bound by any particular theory or mode of
action, intervention in UHR individuals prior to FEP may reduce the risk of developing
10 brain structural abnormalities in the patient and therefore onset of a psychotic disorder.

Psychosocial disability is also associated with psychotic disorders. Much of collateral
psychosocial damage in schizophrenia is known to occur early in the pathogenesis of
the disease, in particular prior to FEP. Thus before a full threshold psychotic disorder
can be diagnosed significant psychosocial disability will have accrued to the individual
15 including loss of function in the workplace or educational arena, (lose peer group school
career professional relationships) and destruction of social networks. Individuals
assessed at UHR for psychosis (or subthreshold psychosis) are often severely
distressed by their symptoms and there is a high risk of suicide in this group.
Accordingly, without being bound by any particular theory or mode of action,
20 intervention in UHR individuals prior to FEP may reduce the severity of psychosocial
disability and consequences of the disability.

It is also therefore contemplated that the intervention according to the invention may be
used to prevent or delay the onset of one or more symptoms of a psychotic disorder.
That is, the severity and number of symptoms which are identified in UHR individuals
25 may be observed to have reduced or regress after the intervention period.

Accordingly, the present invention provides a method of treating pre-psychotic
symptoms in a subject, including administering to the subject a composition including
EPA and DHA.

In a further aspect the present invention provides use of a composition including EPA and DHA for the preparation of a medicament for treating pre-psychotic symptoms in a subject.

As described above, intervention and/or treatment according to the invention involves
5 administration of a composition including EPA and DHA.

Without being bound by any theory or mode of action, the therapeutic effect of omega-3 PUFA may result from altered membrane fluidity and receptor response following their incorporation into cell membranes. Omega-3 PUFA may also interact with the dopaminergic and serotonergic systems. Both systems have been associated with the
10 pathophysiology of schizophrenia. It is generally believed that glutathione, which protects neurons from excitability and oxidative stress, is abnormally low in schizophrenia. EPA may increase glutathione levels in the brain.

Accordingly, the present invention also provides a composition including EPA and DHA when used for the prevention of a psychotic disorder in a subject in need of intervention.

15 In another aspect, the present invention provides a composition including EPA and DHA when used for the treatment of pre-psychotic symptoms in a subject.

Omega 3 fatty acids are an important class of fatty acids, that include eicosapentanoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3). EPA is a highly poly-unsaturated fatty acid (PUFA) which contains 20 carbon atoms and 5 double bonds
20 all in the cis-configuration. The double bonds are located at position 5, 8, 11, 14 and 17. The full chemical name is all cis (or all z) 5, 8, 11, 14, 17-eicosapentanoic acid. DHA is also a PUFA which contains 22 carbon atoms and 6 double bonds all in the cis-configuration. The full chemical name is all cis (or all z) 4, 7, 10, 13, 16, 19-docosahexanoic acid.

25 Typically, dietary sources of DHA and EPA are derived from concentrated fish oils or other sources such as marine micro-organisms or plants. However, it is contemplated that oils used in the composition may be derived synthetically.

In this specification, reference to either DHA or EPA may include a pharmaceutically acceptable derivative thereof. For example, EPA may be in the form of ethyl-EPA, lithium EPA, mono-, di-, or triglyceride EPA or any other ester or salt of EPA, or its free form of EPA.

- 5 Preferably, the unit dosage form of EPA and DHA in the composition includes about 100 to 1000mg. Preferably the composition includes about 700mg of EPA and at least about 480mg of DHA.

The composition is preferably formulated in a unit dosage form by well known methods. The term "unit dosage form" refers to physically discrete units suitable as unitary
10 dosage for the subject, each unit containing a predetermined quantity of active material calculated to produce the desired effect. The final unit dosage form depends in part to the availability of suitable EPA and DHA in suitable concentrations or purity.

In a preferred embodiment of the invention, the final dose of EPA administered to the subject per day is about 700 mg and the final dose of DHA administered to the subject
15 per day is 480mg. The composition may be administered in multiple dosages over the period of the day. For example, 4 capsules may be administered over the course of the day (two in the morning and two in the evening). However, other administration (such as once daily, or twice daily) are not excluded.

Whilst it is possible that EPA and DHA be administered alone, it is preferable that they
20 are administered together in a single composition. When in a single composition, EPA and DHA are present in a ratio of between about 3:1 and 7:5, preferably between about 3:2 and 7:5. Accordingly, preferably the composition includes EPA and DHA (when combined) in a concentration of more than about 50%, preferably more than about 55%, more preferably about 60%.

25 It will be appreciated that other omega-3 fatty acids may also be present in the composition, such as eicosatrienoic acid (ETA), eicsoatetraenoic acid, docosapentaenoic acid (DPA). Other fatty acids (i.e. other than omega-3 fatty acids) may also be present in the composition, for example oleic acid. However, omega-3 fatty

acids will be the major component of the fatty acid content of the composition. Accordingly, preferably the composition includes omega-3 fatty acids in a concentration of at least 50% by weight of total fatty acids present in the composition. Preferably the omega-3 fatty acids are in a concentration of about 51%, 52%, 53%, 54%, 55%, 56%,
5 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%,
72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%,
87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100% by weight of total fatty acids.

The composition may further include a pharmaceutically acceptable carrier, diluent,
10 adjuvant and/or excipient. Each carrier, diluent, adjuvant and/or excipient must be pharmaceutically acceptable such that it is compatible with any other ingredients in the composition and not be injurious to the subject. The use of such carriers, diluents, adjuvants and/or excipients are well known in the art. Supplementary active agents may also be incorporated into the composition. Stabilizer agents or antioxidants may also be
15 included in the composition. Preferably the composition includes Vitamin E.

The composition may be conveniently presented in a unit dosage form and may be prepared by well known pharmacological methods.

The composition is typically administered orally in the form of soft gel capsules. However, other routes of administration (such as topical or as a suppository) are not
20 excluded. Other forms of the composition (such as a syrup, dragee, tablets etc) are not excluded.

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations
25 constitute various alternative aspects of the invention.

EXAMPLE

The following study determined that omega-3 PUFA (EPA/DHA) can reduce psychiatric symptoms and improve psychosocial functioning in UHR individuals preventing a first episode of a psychotic disorder.

5 Participants

Individuals were eligible for participation if they were aged 13 to 25 years and met criteria for one or more of three operationally defined groups of risk factors for psychosis: attenuated positive psychotic symptoms; transient psychosis; and genetic risk plus a decrease in functioning (Table 1). These criteria comprise a combination of trait and state factors which identify people whose risk of becoming psychotic may approach 40% within a 12-month period. These individuals are assessed as being in an Ultra High Risk category for developing a psychotic disorder. These individuals are also referred to as showing pre-psychotic symptoms.

TABLE 1 : Inclusion criteria**Group 1: Attenuated psychotic symptoms**

Presence of symptom scores of 3 on the PANSS delusions scale, 2-3 on the PANSS hallucinations scale, 3-4 on PANSS suspiciousness or 3-4 on PANSS conceptual disorganisation scale (frequency of symptoms ≥ 2 times per week for a period of at least a week and not longer than 5 years, and have occurred within the last year).

Group 2: Transient psychosis

Presence of symptoms scores of ≥ 4 on PANSS hallucinations scale, ≥ 4 on PANSS delusions scale, or ≥ 5 on PANSS conceptual disorganizations scale (symptoms not sustained beyond a week and resolve without antipsychotic medication, and have occurred within the last year).

Group 3: Trait plus state risk factors

Having a schizotypal personality disorder (as defined by DSM-IV) or a first-degree relative with a DSM-IV psychotic disorder and a significant decrease in functioning resulting in a decrease of 30% on the Global Assessment of Functioning Scale from premorbid level, maintained for at least a month and not longer than 5 years. The decrease in functioning needed to have occurred within the past year.

PANSS= Positive and Negative Syndromes of Schizophrenia Scale.

DSM-IV= Diagnostic and Statistical Manual of Mental Disorders

Exclusion criteria included (1) a history of a previous psychotic or manic episode, (2) substance induced psychotic disorder at index presentation, (3) acute suicidal or aggressive behaviour, (4) drug or alcohol abuse that contributed decisively to the index presentation (e.g., dependency on morphine, cocaine, amphetamine, but not cannabis), (5) neurological disorder, (6) IQ<70, (7) structural brain changes in MRI scan (e.g., tumours), except for enlargement of ventricles or sulci, (8) previous treatment with an antipsychotic or mood stabilizing agent (>1 week), (9) taken omega-3 supplements within 8 weeks of being included in the trial, (10) laboratory values more than 10% outside the normal range for transaminases, thyroid hormones, CRP or bleeding parameters, (11) another, severe, intercurrent illness which may put the person at risk or influence the results of the trial, or affect ability to take part in the trial.

Study design

A randomised, double-blind, placebo-controlled 12-week intervention trial of 1.2g per day omega-3 PUFA was undertaken. After randomisation, participants received weekly assessments for 4 weeks, and then at 8, 12 weeks, 6, and 12 months. A computer-generated random sequence based on a block randomised design was administered by an independent third party until all study data were collected. Participants, parents, and

those involved in study interventions, assessing outcomes, data entry and/or data analyses were blind to group assignments. The study was carried out at the psychosis detection unit of the Department of Child and Adolescent Psychiatry, Medical University of Vienna (MUW), Austria. All consecutive referrals between April 2004 and May 2006
 5 were considered for inclusion. The study was approved by the MUW ethics committee (EK-Nr.415/2002), and written informed consent was obtained from all participants (parental or guardian consent was obtained for those <18 years).

Study intervention

The active treatment was a supplement of yellow gelatin 0.5 g fish oil capsules. The
 10 daily dose of 4 capsules provided 700 mg of EPA, 450 mg of DHA, and 7.6 mg of Vitamin E. The total daily dose of other omega-3 fatty acids was 220mg. This provides a daily dose of 1.2 g omega-3 PUFA. Coconut oil was chosen as placebo because it does not contain polyunsaturated fatty acids and has no impact on omega-3 fatty acid metabolism. Placebo capsules were carefully matched in appearance and flavour with
 15 the active treatment. The placebo capsules also contained 10 mg Vitamin E, and 10 mg of fish oil to mimic taste.

The fatty acid composition for the active and placebo capsules used in this study is shown in Figure 1. The fatty acid composition in each of the capsules is outlined in Table 2:

20 **TABLE 2**

Fish Oil capsules		Placebo capsules	
20:5n3	35%	8:0	25%
22:6n3	24%	10:0	71%
18:1n9	14%	20:5n3 plus 22:6n3	<1.5%
18:0	6%	Other fatty acids combined (14:0,	<3%
18:1n7tr	4%		

20:1n9	4%	16:0, 17:0, 18:0, 18:1n7t, 18:1n9t, 18:1n9c, 20:1n9, 22:1n9, 24:1n9, 18:2n6t, 18:2n6c, 18:3n6, 18:3n3, 20:3n6, 20:4n6, 22:2n6, 22:5n3, 22:6n3)	
16:0	3%		
20:4n6	3%		
18:3n3	3%		
17:0	2%		
18:2n6	2%		
20:3n3	1%		
Other fatty acids combined	4%		

Adherence was monitored by pill count and erythrocyte fatty acid quantification. Antipsychotic medication or mood stabilizers were not permitted. Patients could receive antidepressants for moderate to severe depression, benzodiazepines for anxiety, agitation, or insomnia, and needs-based, psychosocial interventions for 12 months.

Outcome measures

The primary efficacy endpoint was conversion to psychosis, based on operationally defined criteria using cut-off points on the Positive and Negative Syndrome Scale (PANSS)¹ (≥ 4 on hallucinations, ≥ 4 on delusions and ≥ 5 on conceptual disorganization), the frequency of positive symptoms (≥ 2 per week), and their duration (≥ 1 week). Secondary measures included the PANSS, the Montgomery Asberg Depression Rating Scale (MADRS)², and the Global Assessment of Functioning (GAF).³ Raters were trained in administration of outcome measures and interrater reliability estimates for PANSS subscales, MADRS, and GAF were excellent (all ICC coefficients > 0.92). The Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P)⁴ was used to ascertain psychiatric diagnoses at baseline and 12-month follow-up. At baseline and 12-week follow-up, fasting erythrocyte fatty acid composition was quantified using capillary gas chromatography after fatty acid extraction from washed erythrocytes. The ratio of

omega-6 to omega-3 fatty acids (omega-6/omega-3) was used to index pre- vs. post-intervention fatty acid composition.¹² Intervention-emergent side effects were assessed with the Udvalg for Kliniske Undersøgelser (UKU).⁵

Statistical analysis

5 The study was powered to detect a 50% reduction in the expected transition rate, corresponding to a transition rate to psychosis (over 12 months) of 20% in the omega-3 group and an anticipated rate of 40% in the placebo group. Power analysis indicated that 75 subjects would provide a 70% chance of detecting such an effect (two-sided alpha level of 0.05). Allowing for 5-10% dropout, we sought to recruit at least 80
10 participants.

All analyses were performed on an intent-to-treat basis. Kaplan-Meier survival analysis assessed differences in time to transition to psychosis between intervention arms at 12-month follow-up using the log-rank test. Estimated survival rates at various points on the survival curve (12-week, 6-, and 12-month) were compared using z-tests. Sensitivity
15 analysis was also performed under the assumption that all participants who were lost to follow-up (n=5) prior the 12-month assessment had converted to psychosis. Number needed to treat⁶ was used to determine the number of individuals needed to be treated with omega-3 PUFA to prevent one individual from progressing to first-episode psychosis.

20 For secondary outcome measures, analyses were carried using the mixed model repeated measures analysis ANOVA (MMRM). The within groups factor was measurement occasion (T0 to T8) and medication group served as the between groups factor. A Toeplitz covariance structure was used to model relations between observations on different occasions. A series of planned comparisons contrasted
25 change from baseline (T0) to 12-week (T6), 6-month (T7), and 12-month (T8) between omega-3 and placebo. MMRM differs from traditional repeated measures ANOVA in that all available data are included in the model and the relationships between different time points is also modelled. Analyses were undertaken using the MIXED procedure in SPSS Version 16.0.

In this trial missing secondary outcome data occurred in two distinct ways. Observations could be missing data due to withdrawal or missed assessments. These observations can reasonably be assumed to be 'missing at random'. The second type of missingness relates to data that are absent following transition to psychosis. Antipsychotic medication was commenced in participants who made the transition to psychosis and no further data were collected after transition. The outcome of interest—the values that participants would have had if active intervention for psychosis had not been initiated and the intervention and observation had continued—is effectively counterfactual. In these circumstances, missingness is not at random and must be explicitly modelled.⁷ A conservative approach was taken to model post-transition outcomes. It was assumed that symptoms and functioning would have been maintained at the transition levels, if antipsychotic medications had not been administered, but would not have further increased.

Differences between intervention groups on categorical variables were analyzed using Fisher's exact test. Independent-samples t-tests were used to compare group differences in baseline-to-12-week omega-6/omega-3 changes in erythrocyte fatty acid composition. Correlational analysis examined associations between baseline-to-12-week omega-6/omega-3 ratio changes and secondary outcome measures.

This study is registered with ClinicalTrials.gov, number NCT00396643.

20 **Results**

Study sample

Eighty-one intervention-seeking individuals were enrolled, 41 were randomly assigned to omega-3 PUFA and 40 to placebo. Both groups had comparable baseline characteristics (Table 3). Three of 41 (7.3%) patients from the omega-3 group, and 2/40 (5.0%) from the placebo group, discontinued the intervention prematurely ($P=0.67$). The remaining 76/81 (93.8%) patients who completed the 12-week intervention, also completed 12-month follow-up for the primary outcome or made a transition to

psychosis during this period; 67/81 (82.7%) completed 12-month follow-up for secondary outcomes (Figure 2).

TABLE 3: Baseline characteristics of participants

	Omega-3 (n=41)	Placebo (n=40)
Age (years)	16.8 (2.4)	16.0 (1.7)
Sex (male)	14 (34%)	13 (33%)
Body-mass index (kg/m²)	21.1 (4.2)	21.4 (3.5)
Tobacco	18 (44%)	24 (60%)
Alcohol		
Less than weekly	23 (56%)	23 (58%)
1 – 6 drinks per week	10 (24%)	11 (28%)
Daily	8 (20%)	6 (15%)
Marijuana		
No	35 (85%)	34 (85%)
Less or equal 2 gram per week	4 (10%)	4 (10%)
More than 2 gram per week	2 (5%)	2 (5%)
Any illicit drug use	6 (15%)	8 (20%)
Psychiatric medication		
Antidepressant	14 (34%)	13 (33%)
Benzodiazepine/sedative	7 (17%)	3 (8%)
Entry criteria		
Attenuated psychotic symptoms	37 (90%)	38 (95%)
Transient psychosis	3 (7%)	2 (5%)
Trait plus state risk factors	4 (10%)	2 (5%)

PANSS score		
Total score	59.9 (13.1)	57.2 (13.9)
Positive subscale	15.0 (3.4)	14.2 (3.1)
Negative subscale	14.1 (5.3)	13.6 (6.5)
General subscale	30.9 (7.2)	29.4 (6.6)
MADRS score	17.6 (8.9)	18.8 (8.7)
GAF score	61.0 (12.0)	60.0 (13.1)
Erythrocyte fatty acids -% of total		
Total saturated	38.4 (4.1)	38.9 (5.0)
Total monosaturated	27.1 (2.6)	27.4 (3.7)
Total omega-6 fatty acids	28.8 (2.8)	28.3 (2.5)
Linoleic (18:2n-6)	6.2 (0.8)	6.3 (1.7)
Arachidonic (20:4n-6)	15.8 (2.2)	15.3 (2.0)
Total omega-3 fatty acids	5.6 (1.2)	5.3 (1.0)
Eicosapentaenoic (20:5n-3)	0.5 (0.2)	0.5 (0.1)
Docosapentaenoic (22:5n-3)	2.2 (0.4)	2.2 (0.4)
Docosahexaenoic (22:6n-3)	2.8 (0.8)	2.5 (0.6)
Family history of psychosis		
Psychosis	10 (25%)	6 (15%)
Non-psychotic bipolar disorder	1 (3%)	0 (0%)
Non-psychotic depression	13 (33%)	12 (31%)
Other psychiatric disorder	11 (28%)	6 (16%)
Data are mean (SD) or n (%). PANSS denotes Positive and Negative Syndrome Scale, MADRS Montgomery Asberg Depression Rating Scale, and GAF Global Assessment of Functioning.		

Efficacy

Primary outcome measure

The cumulative conversion rate to psychosis at 12 weeks was 2.4% (1/41) for omega-3 and 20.0% (8/40) for placebo; at 6 months the rate was 2.4% (1/41) and 27.5% (11/40),
5 and at 12 months the rates were 4.9% (2/41) and 27.5% (11/40), respectively. The risk of progression to psychosis was significantly lower in the omega-3 group than the placebo group over the course of the study ($p=0.009$ at 12 weeks; $p=0.001$ at 6 months and $p=0.004$ at 12 months) (Figure 3). By 12 months the difference between the groups in the cumulative risk of progression to psychosis was 22.6% (95% CI 4.8 to 40.4 with
10 continuity correction). A more rapid conversion time for the placebo group compared with the omega-3 group (log rank test, $\chi^2=7.32$, $p=0.007$) was observed (Figure 3). The sensitivity analysis (log rank test, $\chi^2=4.37$, $p=0.037$) was consistent with the intention-to-treat analysis.

Number needed to treat

15 The number needed to treat with omega-3 PUFA in the study to prevent one individual from progressing to psychosis over a 12-month period was 4 (95% CI 3 to 14) (rounded to the nearest whole number).

Secondary outcome measures

Figure 4 shows mean scores (95% CI) for secondary outcome measures. For post-
20 transition outcomes it was conservatively assumed that symptoms and functioning would have maintained at the transition levels, if antipsychotic medications had not been administered. For the PANSS measures the omnibus interactions between medication group and occasion were not significant (positive, $F[8, 163.5]=1.72$, $p=0.098$; negative $F[8, 162.0]=1.26$, $p=0.268$; global $F[8, 164.2]=1.74$, $p=0.093$; total
25 $F[8, 152.2]=1.66$, $p=0.113$). This reflects the emergence of differences between the groups only later in the trial. Planned comparisons detected between group differences at these times. The omega-3 group had significantly lower PANSS positive, negative,

global, and total scores, at 12 weeks, 6 months, and at 12 months as compared to the control cohort (all $p < 0.05$). There was no significant interaction for the MADRS, and none of the planned contrasts were significant. For the GAF, there was a significant interaction between medication group and occasion, $F(8, 139.8) = 2.99$, $p = 0.004$. At 12 weeks ($p = 0.002$), 6 months ($p = 0.023$), and at 12 months ($p = 0.018$), the omega-3 group demonstrated significantly higher functioning than the control group. Table 4 below shows changes in symptoms and functioning from baseline after 12 months.

TABLE 4: Changes from baseline to 12-month endpoint of secondary outcome measures

	Baseline		Change from baseline		P value*	Effect size†
	Omega-3 (n=41)	Placebo (n=40)	Omega-3 (n=41)	Placebo (n=40)		
PANSS score						
Total	59.9 (2.7)	57.2 (2.7)	-15.7(2.8)	-4.4 (2.8)	0.006	0.70
Positive	15.0 (0.7)	14.2 (0.7)	-4.4 (0.8)	-1.5 (0.8)	0.010	0.69
Negative	14.1 (0.9)	13.6 (0.9)	-3.9 (0.9)	-0.8 (0.9)	0.019	0.52
Global	30.9 (1.4)	29.4 (1.4)	-2.1 (1.5)	-7.5 (1.5)	0.010	0.68
MADRS score	17.5 (1.5)	18.8 (1.6)	-8.1 (1.9)	-5.3 (1.9)	0.291	0.32
GAF score	61.0 (2.3)	60.0 (2.4)	17.7 (2.3)	7.2 (2.3)	0.002	-0.72

Data are mean (SE). PANSS denotes Positive and Negative Syndrome Scale, MADRS Montgomery Asberg Depression Rating Scale, and GAF Global Assessment of Functioning. *P values are based on the contrasts from the repeated measures mixed models analysis. †Difference in change from baseline in units of standard deviations of change.

Fatty acids

Mean (SD) baseline-to-12-week changes in the omega-6/omega-3 ratio in erythrocytes of patients treated with omega-3 and patients given placebo were -2.0 (1.2) and -0.1 (0.7), respectively. There was a significant increase of omega-3 relative to omega-6 in the active intervention group pre- vs. post-intervention, ($t=8.1$, $df=63.3$, $p<0.001$). Pre- vs. post-intervention change in omega-6/omega-3 ratio was significantly associated with a decrease in PANSS global symptoms ($r=0.23$, $p=0.04$) and an increase of the GAF score ($r=-0.27$, $p=0.02$). At the 12-month follow-up, the change in omega-6/omega-3 ratio was significantly associated with an increase of the GAF score ($r=-0.27$, $p=0.03$).

10 No significant associations were observed for other measures. The results of the measurements are shown in Table 5 below.

Adverse events

No statistically significant group differences were observed between omega-3 PUFA and placebo on the UKU (Table 5).

15 **TABLE 5: Side effects from baseline to end-of-intervention (12 weeks)**

	Omega-3 (n=41)	Placebo (n=40)	P Value*
Tension/inner unrest	4 (9.8)	5 (12.5)	0.737
Depression	2 (4.9)	5 (12.5)	0.264
Concentration difficulties	1 (2.4)	5 (12.5)	0.109
Emotional indifference	2 (4.9)	4 (10.0)	0.432
Diarrhea	1 (2.4)	4 (10.0)	0.201
Tension headache	1 (2.4)	4 (10.0)	0.201
Nausea/vomiting	3 (7.3)	3 (7.5)	1.0
Reduced duration of sleep	3 (7.3)	3 (7.5)	1.0
Increased fatigability	3 (7.3)	2 (5.0)	1.0

Failing memory	0 (0-0)	2 (5-0)	0.241
Increased tendency to sweating	0 (0-0)	2 (5-0)	0.241
Orthostatic dizziness	0 (0-0)	2 (5-0)	0.241
<i>Data are number (%). Included are side effects according to the 48-item UKU rating scale that occurred with a prevalence of $\geq 5\%$ in any intervention group. *P values were determined using Fisher's exact test.</i>			

Adherence and concomitant medication

Adherence with study medication (mean) was 81.4% (SD 17.7%) for the omega-3 group and 75.4% (SD 17.8%) for the placebo group ($p=0.13$). Concomitant medication use after randomisation included antidepressants in 5/41 (12.2%) omega-3 patients and 3/40 (7.5%) placebo patients ($p=0.48$), and benzodiazepine in 2/41 (4.9%) omega-3 patient and 1/40 (2.5%) placebo patient ($p=0.57$).

Summary

A randomized, double-blind, placebo-controlled trial tested the efficacy of 1.2 g/day omega-3 PUFA in 81 UHR individuals. Notably, a 12-week intervention period (to test the intervention immediate effect) was followed by a 40-week monitoring period. The conversion rate to psychosis at 12 weeks follow-up (end of intervention) was 2.4% (1/41) for omega-3 and 20.0% (8/40) for placebo ($p=0.009$ at 12 weeks).

Unexpectedly, at 12-month follow-up, 9 months after end of intervention, the rate of conversion to psychosis was still significantly lower in the omega-3 group compared to the placebo group, 4.9% (2/41) vs. 27.5% (11/40), respectively ($p=0.004$ at 12 months).

In contrast to the "wash-out" effect which is typically seen when an active intervention is ceased, we unexpectedly observed a lasting, sustained intervention effect in the group of UHR individuals who received omega-3 compared to placebo beyond the period of intervention. The difference between the groups in the cumulative risk of progression to psychosis was 22.6% (95% CI 4.8–40.4) (Figure 2).

Furthermore, omega-3 PUFA also significantly reduced positive symptoms ($p=0.006$), negative symptoms ($p=0.019$), global symptoms ($p=0.01$), and improved functioning ($p=0.002$) compared to placebo over the total course of the study beyond the intervention period with out showing the usual wash-out effect after intervention with
5 omega-3 was ceased, which was again unexpected (Figure 3).

The incidence of side effects was generally low and did not differ between the intervention and placebo groups at any time over the course of the study.

Omega-3 significantly reduced the transition rate to psychosis and led to significant symptomatic and functional improvements. The magnitude of group differences ranged
10 from moderate (negative symptoms) to moderate-to-large (positive, global and total symptoms, and GAF) (see Table 3). Only one patient on omega-3 intervention developed psychosis during the post-intervention follow-up period. Prodromal symptoms and functioning in patients who received omega-3 did not return to higher levels of severity after the intervention was stopped. These findings are consistent with
15 a preventive, disease progression modifying intervention effect. The high consent rate (76.4%, 81/106) and the low withdrawal rate during the intervention period (6.2%, 5/81) strengthen the results and indicate that omega-3 PUFA were well received by this population.

The finding that intervention with a natural substance may prevent the onset of
20 psychotic disorder provides a potential alternative to antipsychotics for the prodromal phase.

The present results have been obtained in the context of specific risk criteria and should not be generalised to other risk definitions. Psychosis exit criteria were based on progressive positive symptoms, thus potentially including a broader range of psychotic
25 disorders as well as schizophrenia. Although most individuals who converted to psychosis were diagnosed with DSM-IV schizophrenia or schizophreniform disorder at 12-month follow-up (84.6%, 11/13) (see Figure 2), the study aimed to prevent psychotic disorders in general. Strengths of the study include the randomised, placebo-controlled design, the use of standardised inclusion and exit criteria, interrater reliability testing,

the application of an objective compliance measure, the observed correlation between clinical changes with erythrocyte fatty acid composition changes, the robustness of findings across multiple statistical techniques and sensitivity analysis, and last but not least, confirmation at 12-month follow-up by means of SCID-I/P interview that all people
5 who met exit criteria made transitions to genuine psychotic disorders.

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References

1. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale
10 (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-76.
2. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9.
3. Diagnostic and statistical manual of mental disorders, 4th ed.: DSM-IV. Washington, D.C.: American Psychiatric Association, 1994.
- 15 4. First MB, Spitzer RL, Gibbon M, et al.: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). New York, Biometrics Research, New York State Psychiatric Institute, 2002
5. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side
20 effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987;334:1-100.

6. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310:452-4.

7. Henderson R, Diggle P, Dobson A. Joint modelling of longitudinal measurements and event time data. *Biostatistics* 2000;1:465-80.

CLAIMS

1. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for treating pre-psychotic symptoms in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the medicament in a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids in the medicament, the medicament is for administration once per day, wherein the medicament is for administration to the subject for at least 12 weeks, and wherein the subject's risk of transition to psychosis is reduced for at least 9 months after treatment is ceased.
2. The use according to claim 1, wherein the medicament comprises EPA and DHA in a concentration of more than 60% by weight of the total fatty acids.
3. The use according to claim 1 or 2, wherein the medicament is for administration to the subject in a dosage of at least 700 mg EPA and 480 mg DHA per day.
4. The use according to any one of claims 1 to 3, wherein the psychotic disorder is schizophrenia or schizotypal disorder.
5. The use according to any one of claims 1 to 4, wherein the EPA and DHA are in triglyceride form.
6. The use according to any one of claims 1 to 5, wherein the medicament further comprises vitamin E.
7. The use according to any one of claims 1 to 6, wherein the medicament is for use as a sole treatment for the pre-psychotic symptoms.
8. The use according to any one of claims 1 to 7, wherein the subject's risk of transition to psychosis is reduced for at least 12 months.
9. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for intervening treatment in a subject of between about 13 and about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the medicament in a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids, the medicament is for administration once per day, wherein the medicament is for administration to the subject for at least 12 weeks, wherein the

intervening treatment reduces the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder, and wherein the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder is reduced for at least 9 months after the intervening treatment is ceased.

10. The use according to claim 9, wherein the medicament comprises EPA and DHA in a concentration of more than 60% by weight of total fatty acids.

11. The use according to claims 9 or 10, wherein the medicament is for administration to the subject in a dosage of at least 700 mg EPA and 480 mg DHA per day.

12. The use according to any one of claims 9 to 11, wherein the psychotic disorder is schizophrenia or schizotypal disorder.

13. The use according to any one of claims 9 to 12, wherein the EPA and DHA are in triglyceride form.

14. The use according to any one of claims 9 to 13, wherein the medicament further comprises vitamin E.

15. The use according to any one of claims 9 to 14, wherein the medicament is for use as a sole intervening treatment.

16. The use according to any one of claims 9 to 15, wherein the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder is reduced for at least 12 months.

17. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in a unit dosage form for treating pre-psychotic symptoms in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the unit dosage form a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids in the unit dosage form for administration once per day, wherein the unit dosage form is for administration to the subject for at least 12 weeks, and wherein the subject's risk of transition to psychosis is reduced for at least 9 months after treatment is ceased.

18. The use according to claim 17, wherein the unit dosage form comprises EPA and DHA in a concentration of more than 60% by weight of the total fatty acids.

19. The use according to claim 17 or 18, wherein the unit dosage form is for administration to the subject in a dosage of at least 700 mg EPA and 480 mg DHA per day.
20. The use according to any one of claims 17 to 19, wherein the psychotic disorder is schizophrenia or schizotypal disorder.
21. The use according to any one of claims 17 to 19, wherein the EPA and DHA are in triglyceride form.
22. The use according to any one of claims 17 to 21, wherein the unit dosage form further comprises vitamin E.
23. The use according to any one of claims 17 to 22, wherein the unit dosage form is for use as a sole treatment for the pre-psychotic symptoms.
24. The use according to any one of claims 17 to 23, wherein the subject's risk of transition to psychosis is reduced for at least 12 months.
25. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in a unit dosage form for intervening treatment in a subject of between about 13 and about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the unit dosage form in a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids and the unit dosage form is for administration once per day, wherein the unit dosage form is for administration to the subject for at least 12 weeks, and wherein the intervening treatment reduces the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder.
26. The use according to claim 25, wherein the unit dosage form comprises EPA and DHA in a concentration of more than 60% by weight of total fatty acids.
27. The use according to claim 25 or 26, wherein the unit dosage form is for administration to the subject in a dosage of at least 700 mg EPA and 480 mg DHA per day.
28. The use according to any one of claims 25 to 27, wherein the psychotic disorder is schizophrenia or schizotypal disorder.

29. The use according to any one of claims 25 to 28, wherein the EPA and DHA are in triglyceride form.
30. The use according to any one of claims 25 to 29, wherein the unit dosage form further comprises vitamin E.
31. The use according to any one of claims 25 to 30, wherein the unit dosage form is for use as a sole intervening treatment.
32. The use according to any one of claims 25 to 31, wherein the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder is reduced for at least 12 months.
33. The use according to any one of claims 25 to 32, wherein the risk that the subject will experience a first episode of psychosis or develop a psychotic disorder is reduced for at least 9 months after the intervening treatment is ceased.
34. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for treating pre-psychotic symptoms in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the medicament is for administration to the subject for a period of 6 months to arrest the development of pre-psychotic symptoms for at least 12 months after beginning treatment.
35. The use according to claim 34, wherein the use prevents or delays the subject's experience of a first episode of psychosis or the development of a psychotic disorder in the subject.
36. The use according to claim 34 or 35, wherein the EPA and DHA are in a unit dosage form.
37. The use according to any one of claims 34 to 36, wherein the medicament comprises EPA and DHA in a concentration of more than 50% by weight of total fatty acids.
38. The use according to claim 37, wherein the medicament comprises EPA and DHA in a concentration of more than 60% by weight of total fatty acids.
39. The use according to any one of claims 34 to 38, wherein the medicament is for daily administration.

40. The use according to claim 39, wherein the total quantity dose of EPA and DHA for administration to the subject per day is 1.2 g.
41. The use according to claim 39 or 40, wherein the total quantity dose of EPA for administration to the subject per day is 700 mg EPA.
42. The use according to claim 39 or 40, wherein the total quantity dose of DHA for administration to the subject per day is 480 mg.
43. The use according to any one of claims 34 to 42, wherein the psychotic disorder is schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder with psychotic features or major depression with psychotic features.
44. The use according to one of claims 34 to 43, wherein the EPA and DHA are in triglyceride form.
45. The use according to one of claims 34 to 44, wherein the medicament further comprises vitamin E.
46. The use according to one of claims 34 to 45, wherein the medicament is for use as the sole treatment for the pre-psychotic symptoms.
47. The use according to one of claims 34 to 46, wherein the EPA and DHA are present in the composition in a ratio of between 3:2 to 7:5 by weight.
48. The use according to one of claims 34 to 47, wherein the administration of the medicament for the period arrests the development of pre-psychotic symptoms for at least 9 months after treatment is ceased.
49. The use according to any one of claims 34 to 48, wherein the medicament is for administration twice daily.
50. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for intervening treatment in a subject of between about 13 and about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the medicament is for administration to the subject for a period of 6 months to reduce the risk that the subject will transition to psychosis during the 12 months following commencing the administration.

51. The use according to claim 50, wherein the method further results in reduced symptoms and improved functioning beyond the period or reduces the severity of the subthreshold manifestation of psychosis for at least 12 months after beginning treatment.
52. The use according to claim 50 or 51, wherein the EPA and DHA are in a unit dosage form.
53. The use according to any one of claims 50 to 52, wherein the medicament comprises EPA and DHA in a concentration of more than 50% by weight of total fatty acids.
54. The use according to claim 53, wherein the medicament comprises EPA and DHA in a concentration of more than 60% by weight of total fatty acids.
55. The use according to any one of claims 50 to 54, wherein the medicament is for daily administration.
56. The use according to claim 55, wherein the total quantity dose of EPA and DHA for administration to the subject per day is 1.2 g.
57. The use according to claim 55 or 56, wherein the total quantity dose of EPA for administration to the subject per day is 700 mg EPA .
58. The use according to claim 55 or 56, wherein the total quantity dose of DHA for administration to the subject per day is 480 mg.
59. The use according to one of claims 55 to 58, wherein the psychotic disorder is schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder with psychotic features or major depression with psychotic features.
60. The use according to one of claims 55 to 59, wherein the EPA and DHA are in triglyceride form.
61. The use according to one of claims 55 to 60, wherein the medicament further comprises vitamin E.
62. The use according to one of claims 55 to 61, wherein the medicament is for use as the sole intervening treatment to reduce the risk that the subject will transition to psychosis.

63. The use according to one of claims 55 to 62, wherein the subject's risk of transition to psychosis is reduced for at least 9 months after treatment is ceased.
64. The use according to any one of claims 55 to 63, wherein the risk that a subject will transition to psychosis is reduced by at least 22.6%.
65. The use according to any one of claims 55 to 64, wherein the medicament is for administration twice daily.
66. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for increasing functioning in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the medicament in a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids in the medicament, wherein the medicament is for administration to the subject once per day, wherein the medicament is for administration to the subject for at least 12 weeks, wherein the increase in functioning of the subject is assessable, and wherein the subject's functioning remains increased for at least 9 months after treatment is ceased.
67. The use according to claim 66, wherein the medicament increases the functioning of the subject after six months from beginning said treatment.
68. The use according to claim 66 or 67, wherein the medicament increases the functioning of the subject after 12 months from beginning said treatment.
69. The use according to any one of claims 66 to 68, wherein the increase in functioning is assessed using a Global Assessment of Functioning (GAF) scoring system.
70. The use according to claim 69, wherein at 12 months after commencing the use of the medicament, the subject functions at an equivalent of a 78.7 GAF score.
71. The use according to claim 69 or 70, wherein the increase in functioning is equivalent to an increase of at least a 17.7 GAF score.
72. The use of any one of claims 66 to 71, wherein the medicament is for administration to the subject at a dosage of 700 mg EPA and 480 mg DHA per day.
73. The use of any one of claims 66 to 72, wherein the total quantity dose of EPA and DHA for administration per day is about 1.2 g.

74. The use according to any one of claims 66 to 73, wherein the medicament is further for preventing or delaying the subject's experience of a first episode of psychosis or the development of a psychotic disorder in the subject.

75. The use according to claim 74, wherein the psychotic disorder is schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder with psychotic features or major depression with psychotic features.

76. The use of any one of claims 66 to 75, wherein risk that the subject will transition to psychosis is reduced by at least 22.6%.

77. The use of any one of claims 66 to 76, wherein the medicament is for reducing the severity of subthreshold manifestation of psychosis for at least 12 months after beginning the treatment.

78. The use of any one of claims 66 to 77, wherein the EPA and DHA are in triglyceride form.

79. The use of any one of claims 66 to 78, wherein the medicament is for administration twice daily.

80. The use of any one of claims 66 to 79, wherein the medicament includes vitamin E.

81. The use of any one of claims 66 to 80, wherein the intervention period is 6 months.

82. The use of any one of claims 66 to 81, wherein the medicament is for use as a sole medicament for administration to the subject for improving the functioning of the subject.

83. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in a unit dosage form for increasing the functioning in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the EPA and DHA are present in the unit dosage form a ratio of between 3:2 to 7:5, the EPA and DHA together comprise at least 50% by weight of total fatty acids in the unit dosage form for administration once per day, wherein the unit dosage form is for administration to the subject for at least 12 weeks, and wherein the subject's functioning remains increased for at least 9 months after treatment is ceased.

84. The use according to claim 83, wherein the use increases the functioning of the subject after six months from beginning said treatment.

85. The use according to claim 83 or claim 84, wherein the use increases the functioning of the subject after 12 months from beginning said treatment.
86. The use according to claim 83 or 85, wherein the increase in functioning is assessed using a Global Assessment of Functioning (GAF) scoring system.
87. The use according to claim 86, wherein the subject, at 12 months after commencing use of the unit dosage form, functions at the equivalent of a 78.7 GAF score.
88. The use according to any one of claims 83 to 87, wherein the increase in functioning is equivalent to an increase of at least 17.7 in GAF score.
89. The use of any one of claims 83 to 88, wherein the unit dosage form is for administration to the subject at a dosage of 700 mg EPA and 480 mg DHA per day.
90. The use of any one of claims 83 to 89, wherein the total quantity dose of EPA and DHA for administration per day is about 1.2 g.
91. The use according to any one of claims 83 to 90, wherein the unit dosage form is further for preventing or delaying the subject's experience of a first episode of psychosis or the development of a psychotic disorder in the subject.
92. The use according to claim 91, wherein the psychotic disorder is schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder with psychotic features or major depression with psychotic features.
93. The use of any one of claims 83 to 92, wherein risk that the subject will transition to psychosis is reduced by at least 22.6%.
94. The use of any one of claims 83 to 93, wherein the unit dosage form is for reducing the severity of subthreshold manifestation of psychosis for at least 12 months after beginning treatment.
95. The use of any one of claims 83 to 94, wherein the EPA and DHA are in triglyceride form.
96. The use of any one of claims 83 to 95, wherein the unit dosage form is for administration twice daily.
97. The use of any one of claims 83 to 96, wherein the unit dosage form includes vitamin E.

98. The use of any one of claims 83 to 97, wherein the intervention period is 6 months.
99. The use of any one of claims 83 to 98, wherein the unit dosage form is for use as a sole intervening treatment for administration to said subject for improving the functioning of the subject.
100. Use of EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) in the preparation of a medicament for increasing the functioning in a subject of between about 13 to about 25 years of age that meets the ultra-high risk (UHR) criteria for developing a psychotic disorder, wherein the medicament is for administration to the subject for a period of 6 months to increase the functioning of the subject for at least 12 months after beginning treatment.
101. The use according to claim 100, wherein the treatment increases the functioning of the subject after six months from beginning said treatment.
102. The use according to claim 100 or claim 101, wherein the treatment increases the functioning of the subject after 12 months from beginning said treatment.
103. The use according to any one of claims 100 to 102, wherein the increase in functioning is assessed using a Global Assessment of Functioning (GAF) scoring system.
104. The use according to claim 103, wherein the subject, at 12 months after commencing the administration, functions at the equivalent of a 78.7 GAF score.
105. The use according to claim 103, wherein the increase in functioning is equivalent to an increase of at least 17.7 in GAF score.
106. The use according to any one of claims 100 to 105, wherein the medicament comprises EPA and DHA that are present in a ratio of between 3:2 to 7:5 by weight.
107. The use according to any one of claims 100 to 106, wherein the EPA and DHA are in a concentration of more than 50% by weight of total fatty acids.
108. The use of any one of claims 100 to 107, wherein the medicament is for administration to the subject to provide a dosage of 700 mg EPA and 480 mg DHA per day.
109. The use of any one of claims 100 to 108, wherein the total quantity dose of EPA and DHA for daily administration is about 1.2 g.

110. The use according to any one of claims 100 to 109, wherein the medicament is further for preventing or delaying an experience of a first episode of psychosis or development of the psychotic disorder in the subject.

111. The use according to claim 110, wherein the psychotic disorder is schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder with psychotic features or major depression with psychotic features.

112. The use of any one of claims 100 to 111, wherein risk that the subject will transition to psychosis is reduced by at least 22.6%.

113. The use of any one of claims 100 to 112, wherein the medicament is for reducing the severity of subthreshold manifestation of psychosis for at least 12 months after beginning said treatment.

114. The use of any one of claims 100 to 113, wherein the EPA and DHA are in triglyceride form.

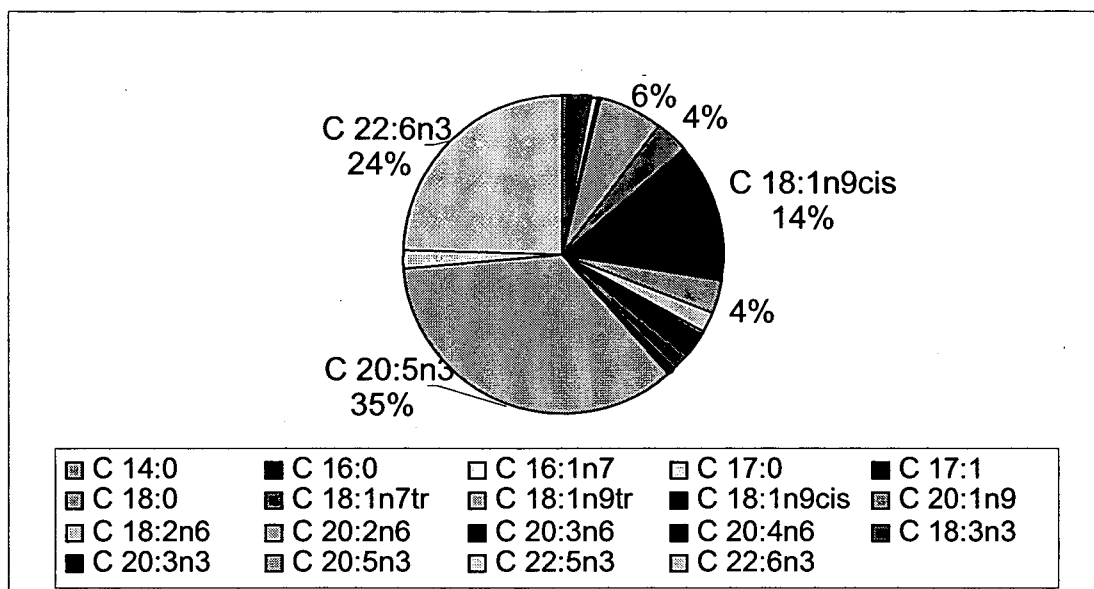
115. The use of any one of claims 100 to 114, wherein the medicament is for administration twice daily.

116. The use of any one of claims 100 to 115, wherein the medicament includes vitamin E.

117. The use of any one of claims 100 to 116, wherein the medicament is for use as a sole medicament for administration to the subject for improving the functioning of the subject.

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(A)



(B)

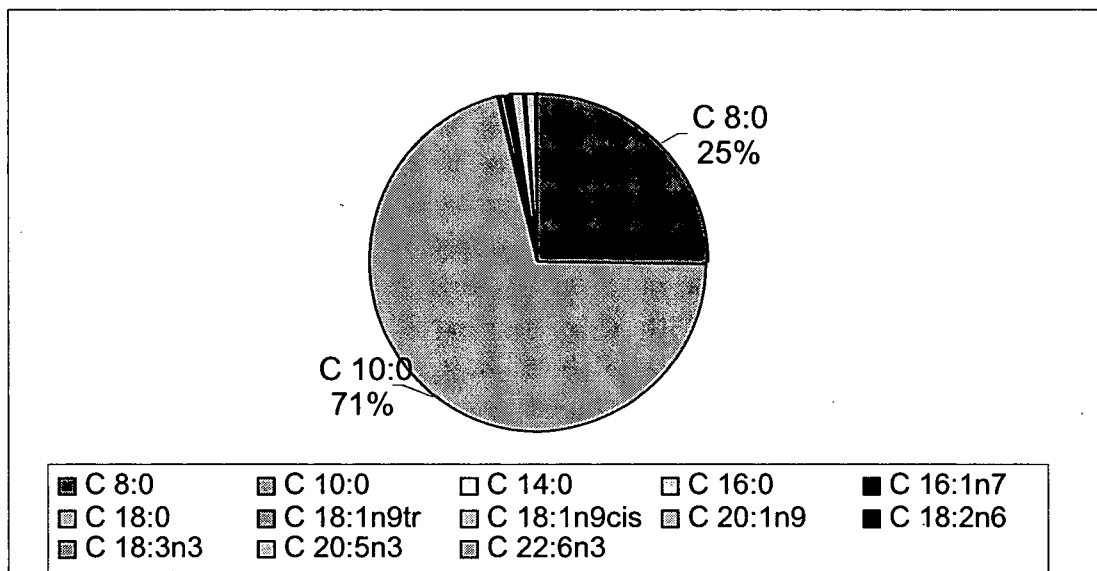


Figure 1

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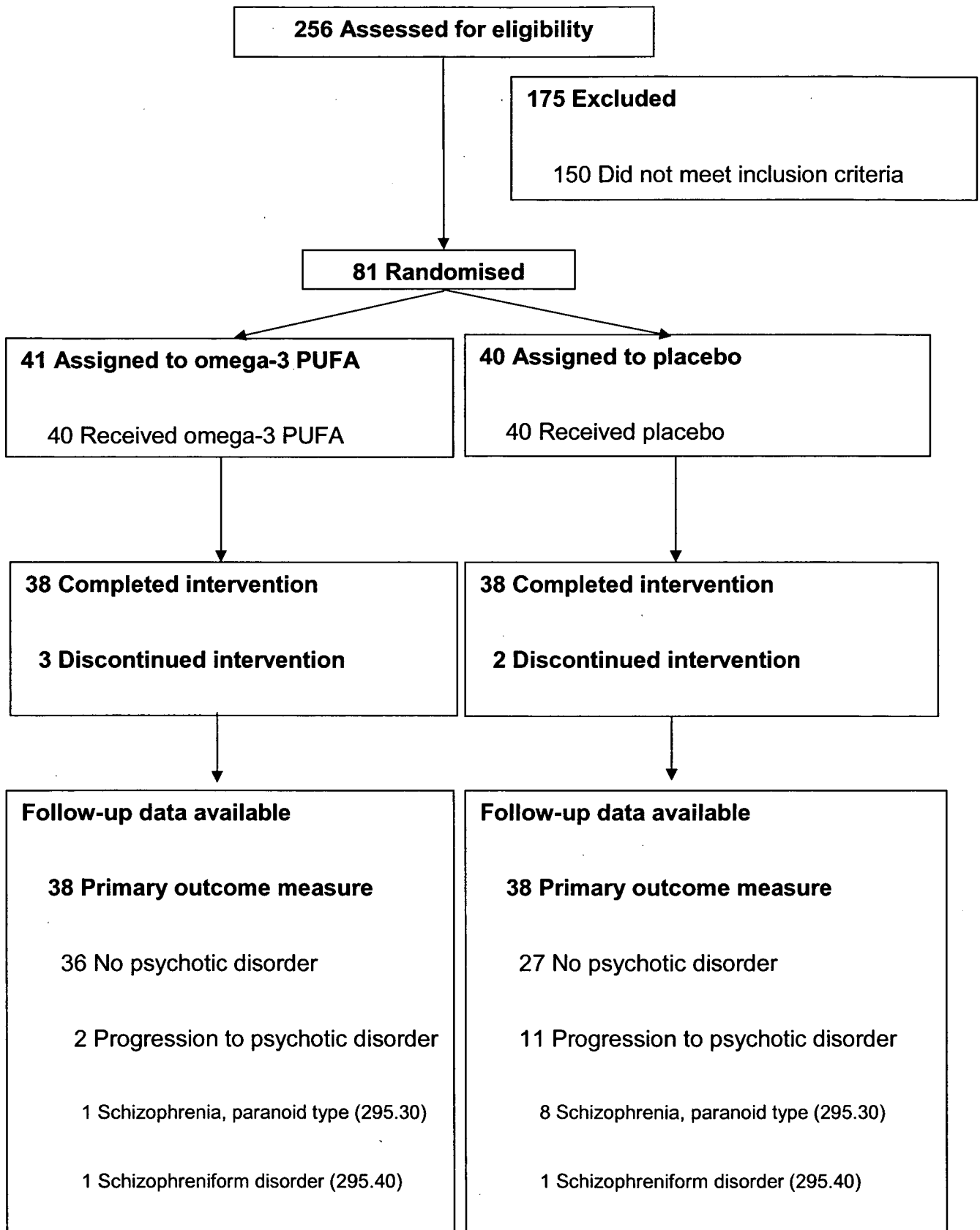


Figure 2

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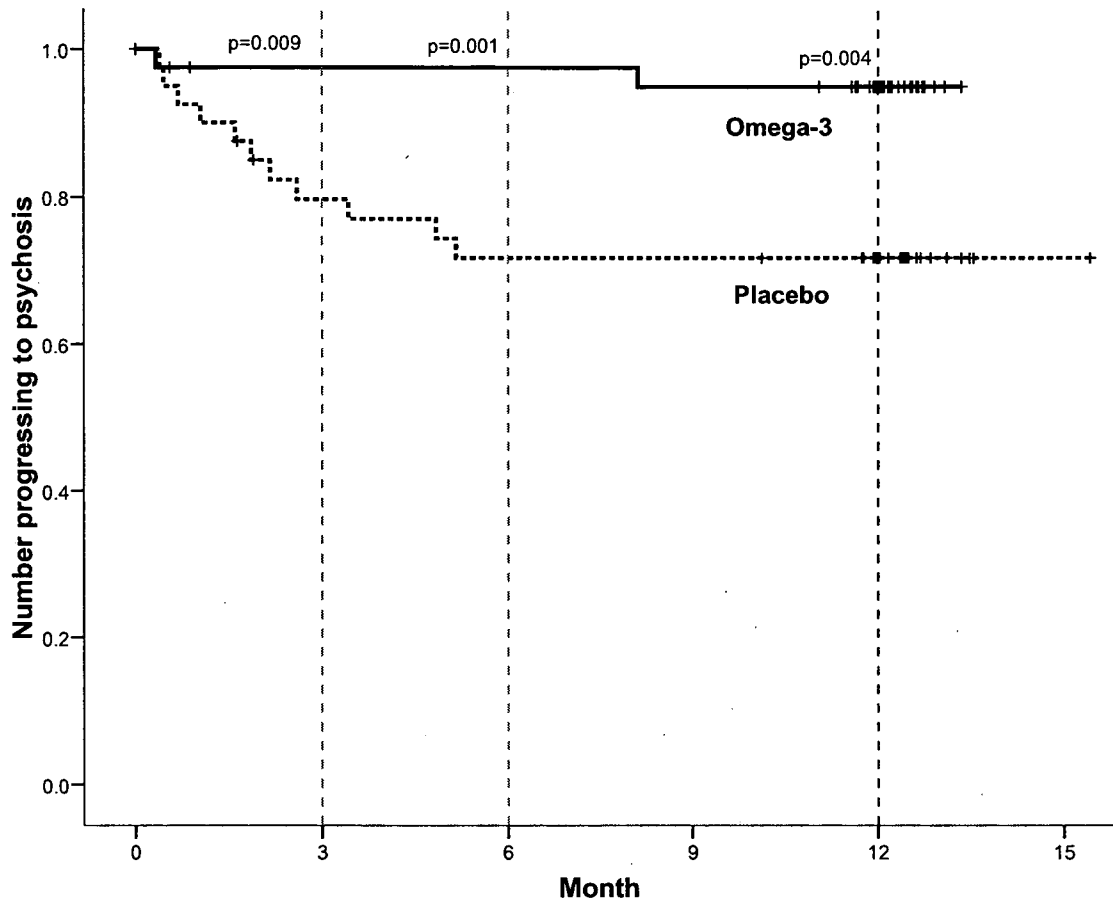


Figure 3

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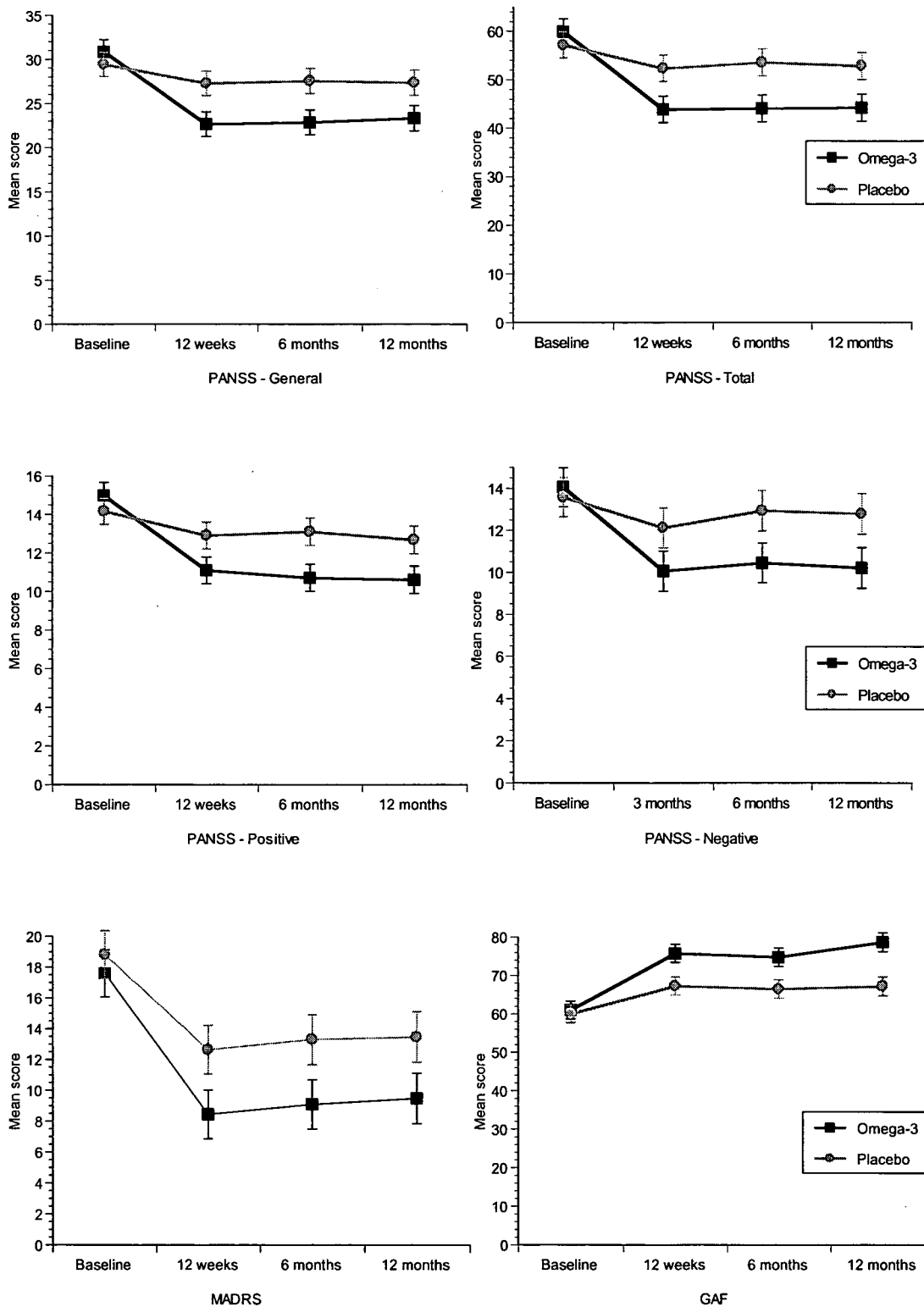


Figure 4

