Research

Final Report

**Project Title:** The Fish Oil Youth Depression Pilot Study. A randomised, double blind, placebo-controlled treatment trial (6515:10659)

**Chief Investigator:** Professor G. Paul Amminger

**Orygen - The National Centre of Excellence in Youth Mental Health**

This research project is funded by
Main Messages

- One hundred thirty eight young people were approached for study participation, 90 (65.2%) of those consented and 48 refused consent.
- Two thirds of eligible young people consented to the trial; those 68 young people were enrolled in the pilot trial.
- More than 80% of the sample completed the 12-week intervention period.
- At the 12-week follow-up, only 25% of participants still reported clinically relevant (moderate or severe) depressive symptoms while 75% of participants were found to have improved clinical symptoms.
- No participant discontinued the trial because of an adverse event.
- We found a randomised controlled trial of omega-3 PUFAs was feasible to be run within headspace centres within existing clinical infrastructure.
- By enrolling 5 participants per month, we were able to show that the recruitment capacity at two headspace centres was sufficient for the trial.
- The findings of this pilot trial indicate a high level of acceptability for omega-3 PUFAs plus cognitive-behavioural case management as first line treatment for major depression in the youth.
Executive Summary

Omega-3 polyunsaturated fatty acids (PUFAs) play an important role in a range of physiological processes in all living organisms, including man. The modern Western diet is low in these essential fatty acids, and supplementation with omega-3 PUFAs (for example, with fish oil) has been shown to have range of beneficial effects on both physical and mental health. This, and the fact that they do not cause any clinically relevant side effects makes omega-3 PUFAs ideal for investigation in young people with emerging depressive symptoms.

Despite the practical importance of the clinical question, no study has investigated supplementation with omega-3 PUFAs in adolescents and young adults up to the age of 25. This pilot study addressed an important clinical question at the first time: can moderate-to-severe major depressive disorder (MDD) in young people aged 15 to 25 be treated with long-chain omega-3 PUFAs (‘fish oil’)? The question has taken on increased clinical importance in the wake of recent evidence questioning the effectiveness and safety of antidepressants in young people, and the subsequent development of treatment guidelines that are equivocal in their support of antidepressant medication as first-line treatment. The National Health and Medical Research Council (NHMRC) Clinical Practice Guideline has recently released its recommendations for the treatment of depressed young people up to the age of 25 (1). It calls for more studies of treatment effectiveness for youth depression, and, in particular, for studies that include the 18- to 25-year old age group. Despite the considerable health burden of depression there are significant gaps in our knowledge on how to treat the illness at its onset.

Omega-3 PUFAs have been shown to be very safe and are free of clinically relevant adverse effects. They have the advantage of excellent tolerability, public acceptance, relatively low costs, and benefits for general health. Epidemiological data linking fish intake with
depression (2-4); observations of alterations in the fatty acid status of people with MDD (2, 5); and RCTs of omega-3 PUFAs in adults with MDD (for reviews see: 2, 6, 7), suggest that omega-3 PUFAs may offer a viable treatment and prevention strategy for depression in young people with minimal associated risk.

In this pilot study we tested the feasibility of a 12-week randomised, placebo-controlled treatment trial of 1.4 grams/day (4 capsules) omega-3 PUFA in 68 young people aged 12-25 years who were experiencing moderate-to-severe depressive symptoms. Specifically we aimed to determine: (1) whether our clients accept first-line treatment with fish oil; (2) the recruitment capacity at two headspace centres for such a trial; and (3) to compare the effect of fish oil and placebo treatment on depressive symptoms to establish an effect size for the intervention to facilitate power calculations for a larger study. The study was conducted at headspace Camperdown (hCD) and headspace Campbelltown (hCT). headspace is an enhanced primary care service for emerging psychiatric disorders. The Brain & Mind Research Institute, University of Sydney holds the contracts for and clinically manages hCD and hCT. Broad inclusion criteria reflected the ‘real world’ clinical characteristics of young people with depression. (i) Age 15-25 years; (ii) help seeking for psychological distress; (iii) a score of $\geq 10$ and $\leq 20$ on the QIDS-C16 (a 16 item measure of depressive symptoms) at first contact with the service AND after 1 week (plus 1-3 days if the client is unable to attend) at the second assessment, OR at 2 subsequent (weekly) follow-up assessments; and (vi) ability to give informed consent and comply with study procedures.

Between 2014 and July 2015, 627 individuals were screened for study eligibility. Of those 250 were ineligible and 225 were not further approached for other reasons (see Figure 1). One hundred thirty eight young people were approached for study participation, 90 (65.2%) of
those consented and 48 refused consent. Three people withdrew their initial consent. After excluding 16 people based of study criteria after completion of their baseline assessment, 68 young people were enrolled in the trial and received the trial interventions. By July 2015, 55 young people were expected to have completed the intervention period. Of those participants, 45 (82%) did so and were successfully followed up 12 weeks after baseline. Ten young people discontinued the intervention (10/68; 15%). Thirteen participants were still in the intervention period by July 2015. The fact that approximately two thirds of eligible young people consented to the trial, and more than 80% of the sample were retained indicates a high level of acceptability for omega-3 PUFAs plus CBCM as first line treatment of depression in the sample.

Research assessments were conducted at baseline, 4, 8, and 12 weeks. Repeated measures analysis indicated significant reductions in depressive symptoms for all pairwise comparisons except for the reduction between week 8 and week 12. At the 12-week follow-up, approximately 25% of participants still reported clinically relevant moderate or severe depressive symptoms while 75% of participants were found to have improved clinical depressive symptoms.

The intervention was found to be safe and effective with 75% of young people showing statistically significant and clinically relevant improvements of their depressive symptoms. No participant discontinued the trial because of an adverse event. This pilot study suggests omega-3 PUFAs is well accepted as a first-line treatment for young people with depression when provided together with a psychotherapeutic treatment whose efficacy versus placebo should be tested in a larger study. The study was also shown to be feasibly conducted within established headspace centres.
The Report

Context

This study aimed to address an important clinical question: can moderate-to-severe major depressive disorder (MDD) in young people aged 15 to 25 be effectively treated with long-chain omega-3 (omega-3) polyunsaturated fatty acids (PUFAs) (‘fish oil’)? The question has taken on increased clinical importance in the wake of recent evidence questioning the effectiveness and safety of antidepressants in young people, and the subsequent development of treatment guidelines that are equivocal in their support of antidepressant medication as first-line treatment. The National Health and Medical Research Council (NHMRC) Clinical Practice Guideline has recently released its recommendations for the treatment of depressed young people up to the age of 25 (1). It calls for more studies of treatment effectiveness for youth depression, and, in particular, for studies that include the 18- to 25-year old age group. Despite the considerable health burden of depression there are significant gaps in our knowledge on how to treat the illness at its onset.

Background

Mental illnesses are the "chronic diseases of the young" (8), and the mental illness that causes most disability in young people is MDD (9). Adolescence and young adulthood form the peak period for the emergence of new cases of depression (10), which will develop into recurrent depression into adulthood for most people (11). The result is that across the lifespan depression causes more impairment (measured in disability-adjusted life years) than any other illness in high- and middle-income countries; and is projected to be the major cause of disability in nations from all income groups by 2030 as the burden of infectious disease declines (12). The rapid developmental increase in the incidence of depression in adolescence and young adulthood, together with evidence that effective treatment can reduce the rate of
recurrence of later depressive episodes (13), means that establishing safe and effective treatments for this age group is of the utmost importance.

The prevalence of MDD by the time a young person reaches 25 is as high as 24% (14). The prevalence increases substantially from puberty; and the peak period for the incidence (or onset of new cases) of depression is the period from 15 to 29 years of age (15). The nature of adolescent-onset depression appears to be quite different to depression that has its onset in childhood. While the prevalence figures for MDD during childhood are similar for boys and girls, from puberty the female-to-male ratio increases to approximately 2:1 (16), and this gender ratio is sustained through adult life. Childhood-onset depression, which is usually a concomitant of an adverse family environment (17), is not a strong predictor of recurrent depression in adulthood (18). Adolescent-onset depression, in contrast, is the start of depression proper: it is often the first episode in life-long recurrent depressive illness. About 70% of people will have a subsequent episode of depression after the first (11) — in part as a consequence of active biochemical processes that are neurotoxic and further catalyse vulnerability (19) — with the result that depression affects a larger proportion of the total life course than any other chronic condition, either physical or mental (20). Youth depression is associated with significant developmental disruption, which has effects through adult life, including lack of educational qualifications, welfare dependency, unemployment, and fewer close friendships and intimate relationships (21-23).

The safety and effectiveness of antidepressants in the treatment of youth depression

In Australia, no antidepressants (including any SSRIs) are currently approved by the Therapeutic Goods Administration (TGA) for the treatment of major depression in children and adolescents aged less than 18 years (24). However, there is ongoing discussion regarding
the use of antidepressants, in particular SSRIs, in young people. Many clinical researchers argue that SSRIs are essential for treating depression in this age group (e.g., 25, 26), while others claim the contrary (27). In 2004, the US Food and Drug Administration (FDA) published the results of a meta-analysis of placebo-controlled trials of SSRIs in more than 4400 children and adolescents aged 12-18 years prescribed SSRIs for the treatment of depressive illnesses, and concluded that the medications doubled the risk of both suicidal ideation and behaviour (4% versus 2%) (28, 29). This led to a ‘black box’ warning by the United States Food and Drug Administration (US FDA) to clinicians about using this class of medication for young people aged up to 24 years to highlight these increased risks in adolescents (30); followed by similar warnings by the Medicines and Healthcare Products Regulatory Agency in the UK (31), the European Medicines Agency (32), and the Therapeutic Goods Administration in Australia (24). In 2006, the US FDA expanded their warning to include young people up to the age of 25 on the basis of an extended examination of placebo-controlled trials that included almost 100,000 patients (29). It is not clear why young people started on antidepressant medication are more likely to develop increased suicidality, though one hypothesis is that they induce mixed symptoms (such as agitation) in depressed patients with latent bipolarity (33). Additional concerns have been raised about the efficacy of antidepressants in young people (e.g., 34). The results of a recent Cochrane systematic review (35) indicate that the only SSRI with consistent evidence of effectiveness in young people is fluoxetine. The effectiveness of fluoxetine however is modest. Paroxetine does not appear to be more effective than placebo. There are inconsistent outcomes for citalopram and sertraline. The NHMRC Clinical Practice Guideline has recently released its recommendations for the treatment of depressed young people up to the age of 25 (1). It calls for more studies of treatment effectiveness for youth depression, and, in particular, for studies that include the 18- to 25-year-old age group.
**Omega-3 PUFAs and MDD**

The rapid expansion in Western populations has been associated with a change in diet, particularly in the last 150 years, with omega-3 PUFAs from fish, wild game, and plants being replaced by saturated fats from domestic animals and omega-6 PUFAs from common vegetable oils (2). These diet changes have led to a large increase in the ratio of omega-6 to omega-3 fatty acids in the general diet from 1:1 to more than 15:1 (36). This has resulted in a high proportion of omega-6 fatty acids (i.e., arachidonic acid) rather than EPA, in the cell membranes of most tissues, leading to increases in inflammatory eicosanoids, which have numerous pathological consequences and are potent promoters of chronic diseases such as atherosclerosis, essential hypertension, obesity, diabetes, arthritis and other autoimmune diseases, and many cancers. In relation to mental health, it has been suggested that the sharp rises in rates of depression and other neurological disorders in the 20th century are being fuelled by increased consumption of vegetable oils rich in omega-6 fatty acids (37, 38). The lower incidence of depression in populations with high intake of marine or sea fish (rich in omega-3 PUFAs) provides support for a link between life-time intake of omega-3 PUFAs and proneness to depression and other psychiatric disorders (3, 39-41), although there are some conflicting results (42-44). As omega-3 PUFAs are essential, one can postulate that major nutritional deficits may interfere with normal brain development and nerve functioning (45), in particular during pregnancy and early childhood, implying that such a deficit may be of importance for the development of psychiatric disorders such as MDD, bipolar disorder or schizophrenia (46). However, there are many confounding factors that may be able to explain the association between low omega-3 PUFAs and depression. It is well known that patients with mental disorders live an unhealthy lifestyle (increased intake of saturated fats, lower intake of omega-3 PUFAs, increased cigarette consumption and alcohol use, less exercise and
more obesity). Therefore it remains unclear if the reduced intake of omega-3 PUFAs has a direct negative impact on the course of the illness or represents an epiphenomenon (4).

Reduced membrane PUFAs in major psychiatric disorders
Omega-3 PUFAs may play a role in the pathogenesis of major affective disorders (47). Alterations in fatty acids in MDD include a low omega-3 PUFA intake, a decrease in omega-3 PUFAs and increased omega-6/omega-3 PUFA ratios in plasma, erythrocytes, adipose tissue and post mortem brain tissue (2, 5, 48). The nature of these fatty acid alterations still has to be elucidated (49). The patterns of fatty acid alterations in MDD patients are not specific for depression but are also found in other (psychiatric) conditions accompanied by increased oxidative stress, e.g. bipolar disorder, schizophrenia, diabetes, Alzheimer’s disease, and are also seen during normal aging (50). Lipid peroxidation data suggest that increased oxidative stress may be one of the mechanisms of reduced membrane omega-3 PUFAs in people with psychiatric disorders such as MDD and schizophrenia (51, 52). In addition, the findings imply that supplementation of PUFAs and/or antioxidants could provide effective treatments for the early stages of depression and other psychiatric disorders.

Treatment studies with omega-3 PUFAs in MDD
Meta-analyses of omega-3 PUFAs for the treatment of mood disorders demonstrate benefits in placebo-controlled trials of unipolar and bipolar depression (2, 6, 7), although heterogeneity of study designs and results has been noted as a methodological concern (53). Studies vary in terms of omega-3 PUFAs used, doses, and durations of trials. Most RCTs have included small numbers of patients who had MDD despite treatment with an antidepressant, with omega-3 PUFAs added as adjunctive treatment. Peet and Horrobin (54) demonstrated a benefit of 1g/d in an RCT (N=70) of 1, 2, or 4 g/d versus placebo in patients
with MDD. Nemets et al (55) also found EPA 2g/d to be more efficacious than placebo in decreasing symptoms of depression in MDD (N=20). Su et al (56) and Silvers et al (57) used combinations of EPA and DHA in patients with MDD with differing results. Su et al demonstrated a benefit of EPA and DHA over placebo (N=28), while Silvers et al did not find a difference between omega-3 and placebo groups (N=77). A recent trial by Grenyer et al (58) of omega-3 fatty acids adjunctive to antidepressants (N=83) did not show a benefit over placebo, although unlike most studies that used a combination of EPA and DHA, the DHA dose was higher than the EPA dose.

Most placebo-controlled studies conducted to date in MDD have been adjunctive studies. A few studies have assessed omega-3 fatty acids as a monotherapy. In one study, DHA (2g/d) for MDD in 36 adults was not significantly more efficacious than placebo (59). In another small monotherapy trial of EPA for MDD (N=57), investigators observed a trend toward efficacy (P=0.087) for EPA 1g/d compared to placebo, with response on the Hamilton Depression Rating Scale as the primary outcome (60). One trial in children (N=28) demonstrated a benefit of omega-3 PUFAs monotherapy (EPA and DHA) compared with placebo (61). In another recent study, investigators assessed omega-3 fatty acids (EPA 1g/d) versus fluoxetine 20mg/d versus the combination of the 2 for MDD in 60 patients (62). EPA and fluoxetine had similar efficacy, with the combination superior to either alone.

In summary, positive studies of omega-3 PUFAs in mood disorders have generally shown efficacy for treatment with EPA alone or EPA and DHA in combination (with EPA present in greater doses than DHA). Side effects of the recommended doses of omega-3 PUFAs in MDD are relatively minor and include mild gastrointestinal discomfort, most commonly burping or unpleasant taste. Although increased bleeding is a theoretical risk, no actual cases of bleeding
have been reported, even though there have been high-dose trials in which patients were medically compromised, postoperative, and/or using concomitant anticoagulants. Doses of 1 to 9 g/d of omega-3 PUFAs have been studied in mood disorders, with a majority of evidence supporting doses in the lower end of this range. A dose-finding study using 3 doses of DHA monotherapy demonstrated greater efficacy at 1 g/d compared to 2 g/d and 4 g/d (60), consistent with the findings of an RCT of ethyl-EPA as adjunctive treatment in MDD that showed greater benefit at lower doses (54). Adjunctive EPA or the combination of EPA and DHA appear most useful, with less evidence for DHA alone. However, the general health benefits of omega-3 PUFAs, epidemiologic evidence, modest efficacy data in MDD, and low risks make omega-3 PUFAs a reasonable treatment strategy for moderate to severe depression in particular in young people.

Study design issues

Despite the practical importance of the clinical question, no study has investigated supplementation with omega-3 PUFAs in adolescents and young adults up to the age of 25. Studies such as TADS (63) and ADAPT (64) enrolled depressed patients from late childhood up to mid-adolescence; and by including patients in pre-pubertal, peri-pubertal and post-pubertal development periods likely increased the heterogeneity of the depression being investigated. The period from post-puberty to 25 years of age is continuous in a neurodevelopmental sense — studies show that important brain maturational processes start from puberty and continue up to the age of 25 (65) — and as the peak period for the onset of first episodes of depression (15), it is a key time for effective interventions. The importance of studies that include patients in this age range has been further emphasised by the FDA’s extension of its ‘black box’ warning to patients up to the age of 25.
Approach

Study design

We conducted a 12-week, double blind, randomised-control pilot trial in which 68 participants with moderate-to-severe MDD were allocated to treatment with either omega-3 PUFAs plus CBCM or Placebo plus CBCM. The study was approved by the University of Sydney ethics committee, and conducted in accordance with Good Clinical Practice guidelines. Written informed consent was obtained from all participants (parental or guardian consent was obtained for those aged of 18 years). The protocol addressed all of the applicable CONSORT 2010 Statement checklist items that pertain to trial methodology. The trial was registered at the Australian New Zealand Clinical Trials Registry: ACTRN12613001352796.

Setting

The study was conducted at headspace Camperdown (hCD) and headspace Campbelltown (hCT). Clinical services at these headspace centres were delivered by a multidisciplinary group of clinicians: nurse, occupational therapists, social workers, clinical psychologists and psychologists, GPs and psychiatrists. headspace is an enhanced primary care service for emerging psychiatric disorders and there is a significant number of patients who do not get seen by a psychiatrically qualified medical practitioner during their episode of care. The Brain & Mind Research Institute, University of Sydney holds the contracts for and clinically manages hCD and hCT.

Study criteria

Inclusion criteria: Broad inclusion criteria reflected the ‘real world’ clinical characteristics of young people with depression. (i) Age 15-25 years; (ii) help seeking for psychological distress; (iii) a score of ≥10 and ≤20 on the QIDS-C17 (a 17 item measure of depressive
symptoms) (66) at first contact with the service AND after 1 week (plus 1-3 days if the client is unable to attend) at the second assessment, OR at 2 subsequent (weekly) follow-up assessments; and (vi) ability to give informed consent and comply with study procedures.

**Exclusion criteria:** (i) Lifetime diagnosis or history of treatment for psychotic disorder or bipolar disorder or substance dependence (assessed with a brief questionnaire); (ii) history of treatment with an antidepressant (more than four weeks during the last 12 months); (iii) acute suicidal behaviour (score of 6 on Comprehensive Assessment of At Risk Mental States (CAARMS) item 7.3) (67) or aggressive behaviour (score of 6 on CAARMS item 5.4); (iv) being at ultra-high risk for psychosis (defined by CAARMS); (v) depression secondary to a medical condition; (vi) pregnancy or lactation; (vii) abnormal liver function, thyroid function or haematological findings; (viii) individuals who are taking omega-3 supplements or psychotropic medication, currently or within 8 weeks of being included in the trial, for more than 1 week.

**Withdrawal criteria:** (i) A serious adverse event occurs, in particular, ongoing diarrhoea or other severe gastrointestinal symptoms (>1 week) or an allergic reaction to the study medication; (ii) acute suicidal behaviour (score of 6 on CAARMS item 7.3) or aggressive behaviour (score of 6 on CAARMS item 5.4) during the 12-week intervention period; (iii) a person is hospitalised for psychiatric reasons; (iv) a person is started on omega-3 supplements; (v) the randomisation code is broken.

**Exit criteria:** a person exits the trial (i) by having a score of >20 on the QIDS-C17 over 4 weeks; (ii) by developing a first-episode of a psychotic disorder or mania (both defined by the CAARMS – i.e. threshold symptoms for at least 1 week); (iii) by being commenced on
psychotropic medication (e.g., antidepressant, antipsychotic or mood stabiliser). People who exit the trial are offered to continue on the trial medication for up to 12 weeks while active treatments (e.g., antidepressant, antipsychotic or mood stabiliser) are commenced. Further research assessments will be carried out for the total length of the trial. The data collected past meeting the exit criteria will not be included in the primary analysis.

**Interventions**

**Treatment time-points:** Participants received either omega-3 PUFAs or Placebo for 12 weeks. The experimental intervention was provided in addition to 5 sessions (mean) of cognitive-behavioural case management (CBCM) which were offered as part of the study by a therapist during the 12-week intervention period. Depending on the participant’s needs (additional sessions were provided). If a participant met exit or withdrawal criteria, and after the 12-week intervention period, standard care (treatment as usual) was provided by headspace clinicians. For the purposes of the study analyses, ‘entry’ was considered to be the date the participant commenced the study medication. However, participants were only included in the study after they had fulfilled the eligibility criteria and were randomised to one of the interventions described below.

**Cognitive-behavioural case management (CBCM):** CBCM consists of cognitive-behavioural therapy (CBT) embedded within case management. The treating clinicians used a specifically developed manual that details the CBCM to be delivered in the trial, and which outlines the minimum standard of treatment to be delivered. The number of sessions delivered was captured for each client. Any additional interventions delivered were also documented.
**Experimental intervention:** The active treatment was a supplement of yellow gelatine 0.625 g capsules containing concentrated marine fish oil. The daily dose of 4 capsules provided approximately 700 mg of eicosapentaenoic acid (EPA, 20:5n3), 480 mg of docosahexaenoic acid (DHA, 22:6n3), and 7.6 mg of Vitamin E. Paraffin oil was chosen as placebo because it does not contain PUFAs and has no impact on omega-3 PUFA metabolism. To ensure blinding, placebo capsules were carefully matched in appearance and flavour with the active treatment; they also contained the same amount of Vitamin E as the fish oil capsules, and 1% fish oil to mimic taste.

**Outcome measurements**
Assessments were completed at the initial assessment, baseline (i.e., prior to randomisation), and at 4, 8 and 12 weeks of the trial. The primary outcome measure is change in depressive symptoms at 12 weeks, which was assessed with the 17-item clinician-rated version of the QIDS. The QIDS is a recently developed scale (66) that assesses the criterion symptom domains for DSM-IV MDD. The scale has been shown to be a reliable tool for assessing adolescent depression (68), making it one of the few depression scales that have been validated across adolescent and adult populations.

**Management of Risk**
The trial therapist or a psychiatric registrar assessed participants every week during, and until 2 weeks after, the intervention period of the trial for the presence of suicidal ideation and harm-related behaviours. A record was made of any adverse event that arises during the trial. An adverse event was defined as any unfavourable medical change that is accompanied by functional or clinical impairment, which may or may not be related to the study treatment. In this study, any undesirable medical condition occurring from the time of signing consent
(even if no study treatment or pharmaceutical product has been administered) was considered to constitute an adverse event. Adverse events were recorded using the Antidepressant Side-Effect Checklist (ASEC) (69). Patients usually find omega-3 PUFAs highly tolerable. In our previous psychosis prevention RCT, 94% of participants completed the 12-week intervention period (70). In order to assure the safety of the study participants, we assessed risk (i.e., suicidal behaviour and aggressive behaviour) weekly throughout the 12-week intervention period; this was a study withdrawal criterion (see: Withdrawal criteria).

Data analysis

We applied frequency data and descriptive statistics (means and standard deviations) to assess demographic and clinical information. For comparisons of categorical variables, we calculated chi-square statistics, applying Fisher’s exact test when cell sizes were small. Student’s t tests were used to compare groups for continuous variables. Repeated measures analysis was used to examine how depression changed over time. A significance level of 0.05 was used for all statistical tests, and two-tailed tests were applied.

Results

Sample

Between May 2014 and July 2015, 68 individuals (24 males; 44 females) were randomised and enrolled in the trial (Figure 1). The mean age of the study participants at baseline was 20.06 (SD 2.61; range 15 – 25) years. The mean age in males and females was 20.78 (SD 2.86) and 19.66 (SD 2.41) years (t test: t=1.73, p=0.088), respectively.
Figure 1. Enrolment and outcomes flowchart

**Total screened (n=627)**
- Headspace Camperdown (n=500)
- Headspace Campbelltown (n=127)

**Ineligible / Excluded (n=250)**
- Hx of psychotic, bipolar, substance dependence disorder
- Hx of antidepressant Tx (> 4wks over last year)
- Acute suicidal or aggressive behavior
- Depression sec. to medical condition
- IQ<70
- Pregnancy / lactation
- 15% outside normal bleeding
- Already taking omega-3 or antidepressant

**Consent refused (n=48)**
- Doesn’t want fish oil
- Definitely wants fish oil
- Not interested in research
- Insufficient time
- Other / unknown

**Not approached for study (n=225)**
- Disengaged or lost to follow-up
- Already in therapy
- Moved out of area
- Out of catchment area
- Needs after-hours
- Other or unknown

**Approached for the study (n=138)**

**Consented but discontinued before randomized (n=3)**
- Lost to follow-up
- Consent withdrawn

**Consented received (n=90)**

**Pending (n=13)**
- Attempting to contact YP (n=14)
- Consent being considered (n=2)

**Ineligible after baseline (n=16)**

**Baseline completed (n=87)**

**Total randomised (n=68)**
- headspace Camperdown (n=51)
- headspace Campbelltown (n=17)

**Withdrew consent after baseline (n=3)**

**Expected by 31 July 2015: (n=55)**
- Completed Week 12 (n=45)

12-week retention rate:
\[
\frac{45}{55} = 0.82
\]

**Still in the RCT (n=13)**

**Discontinued intervention (n=10)**

**Met exit criteria (n=4)**

**Met withdrawal criteria (n=0)**
Is fish oil an acceptable treatment to young people with depression?
We assessed the feasibility of a 12-week treatment with 1.4 grams/day (4 capsules) omega-3 PUFA or placebo in young people aged who were experiencing moderate-to-severe depressive symptoms. Between May 2014 and July 2015, 627 individuals were screened for study eligibility. Of those 250 were ineligible and 225 were not further approached for other reasons (see Figure 1). One hundred thirty eight young people were approached for study participation, 90 (65.2%) of those consented and 48 refused consent. Six people withdrew initial consent. After excluding 16 people based of study criteria after completion of their baseline assessment, 68 young people were enrolled in the trial and received the trial interventions. By July 2015, 55 young people were expected to have completed the intervention period. Of those 45 (82%) were successfully followed up 12 weeks after baseline. The fact that 65% (90/138) of eligible young people consented to the trial, and 66% (45/55) of the sample were retained after the intervention indicates a high level of acceptability for omega-3 PUFAs plus CBCM as first line treatment of depression. On average 5 participants per month was recruited into the study from 2 headspace centres.

Depressive symptoms at baseline
At baseline the QIDS total mean score in the study sample was 13.8 (SD 2.2). No statistical difference was found for the QIDS total score between males and females (13.8 v 13.9).

Table 1. Means and SDs for QIDS items at baseline in 68 young people

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<th>Maximum</th>
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<td>.0</td>
<td>3.0</td>
<td>1.8</td>
<td>.9</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>68</td>
<td>.0</td>
<td>3.0</td>
<td>.5</td>
<td>.8</td>
</tr>
<tr>
<td>Involvement</td>
<td>68</td>
<td>.0</td>
<td>3.0</td>
<td>1.1</td>
<td>.9</td>
</tr>
<tr>
<td>Energy / Fatigability</td>
<td>68</td>
<td>.0</td>
<td>3.0</td>
<td>1.8</td>
<td>.5</td>
</tr>
<tr>
<td>Psychomotor Slowing</td>
<td>68</td>
<td>.0</td>
<td>2.0</td>
<td>.9</td>
<td>.8</td>
</tr>
<tr>
<td>Psychomotor Agitation</td>
<td>68</td>
<td>.0</td>
<td>2.0</td>
<td>.7</td>
<td>.7</td>
</tr>
</tbody>
</table>
At 12 weeks, approximately only 25% of participants reported clinically relevant moderate to very severe depressive symptoms.

At baseline more females (29.5% 13/44) than males (16.7%; 4/24) had severe depressive symptoms when enrolled in the study. A chi-square test did not indicate a statistically significant group difference (p=0.24). At 12-week follow-up, the rates for QIDS categories were very similar for males and females with no statistically significant differences (Table 2).
Change in depressive symptoms

Depressive symptoms improved statistically significant and clinically relevant within the first 4 weeks of the intervention (QIDS total scores: week 0 = 14.0; week 4 = 10.1). Notably, depressive symptoms further continued to decrease (see Figure 3).

Figure 3: Mean scores for depressive symptoms at baseline, 4, 8 and 12-weeks

<table>
<thead>
<tr>
<th>QIDS Categories (Week 12)</th>
<th>No Depression</th>
<th>Count</th>
<th>Sex</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>% within Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Depression</td>
<td></td>
<td>10</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td>12</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>% within Sex</td>
<td></td>
<td>34.5%</td>
<td>37.5%</td>
<td>35.6%</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>% within Sex</td>
<td></td>
<td>17.2%</td>
<td>12.5%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>% within Sex</td>
<td></td>
<td>6.9%</td>
<td>6.3%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Very severe</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>% within Sex</td>
<td></td>
<td>0.0%</td>
<td>6.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>29</td>
<td>16</td>
<td>45</td>
</tr>
<tr>
<td>% within Sex</td>
<td></td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
More specifically as shown in Table 2, a repeated measures analysis indicated significant reductions in depressive symptoms for all pairwise comparisons except for the reduction between week 8 and week 12.

Table 2. Results of the repeated measures analysis with the QIDS total score as the dependent variable

<table>
<thead>
<tr>
<th>Measure: MEASURE_1</th>
<th>Mean Difference (I-J)</th>
<th>Std. Error</th>
<th>Sig</th>
<th>95% Confidence Interval for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>3.90</td>
<td>.60</td>
<td>.000</td>
<td>2.69</td>
</tr>
<tr>
<td>2</td>
<td>-3.90</td>
<td>.60</td>
<td>.000</td>
<td>-5.11</td>
</tr>
<tr>
<td>3</td>
<td>1.55</td>
<td>.69</td>
<td>.031</td>
<td>.15</td>
</tr>
<tr>
<td>4</td>
<td>2.68</td>
<td>.86</td>
<td>.003</td>
<td>.94</td>
</tr>
<tr>
<td>1</td>
<td>-5.45</td>
<td>.70</td>
<td>.000</td>
<td>-6.87</td>
</tr>
<tr>
<td>2</td>
<td>-1.55</td>
<td>.69</td>
<td>.031</td>
<td>-2.95</td>
</tr>
<tr>
<td>4</td>
<td>1.13</td>
<td>.69</td>
<td>.109</td>
<td>.26</td>
</tr>
<tr>
<td>4</td>
<td>-6.58</td>
<td>.83</td>
<td>.000</td>
<td>-8.26</td>
</tr>
<tr>
<td>2</td>
<td>-2.66</td>
<td>.86</td>
<td>.003</td>
<td>-4.41</td>
</tr>
<tr>
<td>3</td>
<td>-1.13</td>
<td>.69</td>
<td>.109</td>
<td>-2.51</td>
</tr>
</tbody>
</table>

Based on estimated marginal means

* The mean difference is significant at the
b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Column 1 and 2: 1 = baseline, 2 = 4 weeks, 3 = 8 weeks, 4 = 12 weeks

Treatment effect of omega-3 PUFAs

Originally this pilot study also aimed to establish an effect size for the intervention to facilitate power calculations for a larger study. However, during this trial we received funding for a larger trial for 300-400 people. This pilot study was used to assess the acceptability and feasibility of the trial. As these objectives were successful, it was decided not to break blinding of allocation to active and placebo arms so that data from the participants in the pilot trial could augment the larger trial. Therefore we are not in a position to compare the effect of fish oil and placebo treatment on depressive symptoms at this stage. The larger trial will determine if omega-3 PUFAs is an effective treatment for youth depression (71).
References

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