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Evaluation of the effect of omega-3 fatty acids in the treatment of premenstrual syndrome: ''A pilot trial''

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Summary

Introduction: Premenstrual syndrome (PMS) refers to a cyclic appearance of somatic and psychiatric symptoms that affect some women. Finding an effective and safe method for the treatment of PMS has always been a serious concern, because approximately 40% of women report PMS, and in 2–10% of cases it is severe enough to affect their life style and job.

Objective: The purpose of the present study is to evaluate the effect of omega-3 fatty acids on the treatment of PMS.

Method: A randomized double blind controlled trial was performed on 184 eligible women. The eligible women were randomly assigned into two groups. The number of women who have finalized the study with us was 124.

In the case group (omega-3 group = group A, $n = 70$), omega-3 in an amount of 2 g was prescribed for a one per day basis on a single dosage (two 1 g pearls), and in the control group (placebo group = group B, $n = 69$) 2 placebo soft gel, which were completely similar to omega-3 soft gels, were prescribed.

The severity and duration of each of the symptoms were compared in both groups 1.5 and 3 months after the beginning of treatment.

Results: There were no significant differences between the two groups according to age, BMI, level of education, and the severity and duration of primary symptoms.

After 45 days from starting omega-3, the mean severity of depression ($P = 0.03$), anxiety ($P = 0.02$), lack of concentration ($P = 0.03$) and bloating ($P = 0.02$) in the case group, were all significantly lower than in the control group.

The duration of depression ($P = 0.04$) and bloating ($P = 0.031$) in the case group were less than in the control group.

After 90 days from starting the treatment, the mean severity of depression ($P = 0.007$), anxiety ($P = 0.004$), lack of concentration ($P = 0.009$), bloating ($P = 0.004$), nervousness ($P = 0.01$) and the duration of depression ($P = 0.01$), nervousness ($P = 0.02$), anxiety ($P = 0.03$), lack of concentration ($P = 0.02$), bloating ($P = 0.004$), headache ($P = 0.04$) and breast tenderness ($P = 0.02$) were all lower in the case group.

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Conclusion: It appears that omega-3 fatty acids may reduce the psychiatric symptoms of PMS including depression, nervousness, anxiety, and lack of concentration and may also reduce the somatic symptoms of PMS including bloating, headache and breast tenderness. These effects increased by longer duration of treatment.

Introduction

Premenstrual syndrome (PMS) is defined as the cyclic occurrence of mood and/or behavioural changes, which start during the secretary or premenstrual phase of the menstrual cycle and recover at the beginning of menstruation.[1]

Approximately 40% of women report PMS, but in 2—10% of cases it is severe enough to affect their lifestyle and work.[1,2]

From the first expression of this disorder in 1931 till the present day, because of the real unknown causes,[1] different and varied treatments have been suggested, these based on aetiological hypotheses including low progesterone levels, high oestrogen levels, falling oestrogen levels, changes in the oestrogen/progesterone ratio, increased aldosterone activity, increased rennin—angiotensin activity, increased adrenal activity, endogenous opiate withdrawal, subclinical hypoglycaemia, central changes in catecholamines, responsiveness to prostaglandins, vitamin deficiencies and excess prolactin secretion.[1]

The main purpose of treatment is to control the symptoms enough to free the women of tension and pain and to be able to work appropriately throughout the entire menstrual cycle.[1]

Amongst the most important of these drugs are hormonal agents such as oral contraceptive pills, danazol, GnRH agonists, anti-progesterone RU 486, and anti-anxiety agents, tri-cyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), diuretics, prostaglandin inhibitors, dietary supplementations and vitamin B_6.[1,3,4] Because the women may need treatment in the long term, a drug that is both safe and inexpensive should be used.[1]

Omega-3 fatty acids are one of the agents that have been proposed for the relief of symptoms of PMS.

There are two main forms of omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[5] Omega-3 fatty acids may act as anti-inflammatory agents and reduce the conversion of arachidonic acid to prostaglandin $F_2\ \alpha$ (PGF_2() and therefore, increase the level of prostaglandin I_2 (PGI_2) which has less inflammatory action.[5,6]

Omega-3 fatty acids are among essential dietary agents. Their level in most ordinary food of the American people is very low.[6] They can be increased in the food by changing diet, and by adding them as a supplement.

In some studies,[5] omega-3 fatty acids have been found to be effective in different cases of psychiatric disorders. A study on EPA could not show any effect on PMS[7] however; some other studies evaluated the effect of omega-3 fatty acids through fish oil for the treatment of mild cases of depression.[8] Therefore, it may be an acceptable method of treatment for PMS as one of its symptoms is mood depression.[9]

The adverse effects are rare but they sometimes may cause nausea, diarrhoea and belching with a bad taste in the mouth.[6]

Unfortunately, there are not many studies on the effect of omega 3 fatty acids on PMS, and to the best of our knowledge, this is the first study on this subject.

The purpose of the present study is to evaluate the effect of omega-3 fatty acids for the relief of the symptoms of PMS. Because the placebo effect is also very important in the management of patients, this study has been performed in comparison with placebo.

Materials and methods

A randomized, double-blind clinical trial was performed in Tehran, Iran, between October 2009 and March 2010 on university students who suffered from PMS. It was performed as an exploratory pilot trial.

Inclusion criteria were: age between 20 and 45 years, educational level more than high-school, normal menstrual cycle and bleeding during previous 3 months (3—7 days of bleeding), body mass index (BMI) between 19 and 26, regular menses and having PMS, according to a questionnaire and recording the symptoms for 3 consecutive cycles.

Exclusion criteria were: breast feeding and pregnancy, any history of psychiatric disorders or drug use, smoking or alcohol consumption, any systemic disorder, oral contraceptive pill usage, allergy for sea foods and coagulopathy, using dietary or other supplementation, special impressive events, such as marriage, family bereavement, surgical operations 3 months before entering the study, primary or secondary amenorrhoea and immigrants (because all of these may have effect on women and cause the symptoms such as PMS).

The study was performed as an exploratory pilot trial. The objective of the study was to evaluate the effectiveness of omega 3 for the management of PMS and to compare the effectiveness of omega 3 for the management of PMS with that of placebo.

The diagnosis of PMS was confirmed in an interview, and after selection of the cases a diagnostic questionnaire, based on diagnostic criteria of The American College of Obstetrics and Gynaecology, was fulfilled for 3 consecutive months before entering the study. The women should have one or more somatic or mood symptoms for 5 days before beginning of menstruation, in her three previous cycles, which cease at the onset of menstruation.

Mood symptoms include depression, nervousness, jitteriness, anxiety, dizziness and low concentration and being incapable of social activity. Somatic symptoms included breast tenderness, bloating, headache and oedema.

The symptoms should have recovered during the first 4 days of menstruation and not to start until day 13 of the cycle.

A visual analogue score (VAS) was used to evaluate the severity of each of the symptoms. A written informed consent was obtained from all participants and they were fully informed about the study, and institutional review board approval and also institutional ethics committee approval was given to the study. The study was conducted as a randomized, double-blind clinical trial.

Each patient was asked to take two 1-g soft gels of omega-3 (DHA 12% and EPlA 18%). The placebo was completely similar to this pearl in shape, taste and smell, and had been made by the same manufacturer and it was free of oil (Zahravi, Tabriz, Iran). They were provided free of charge for all of patients. The pearls were named A and B by the manufacturer, were then given to the researcher and after finishing the statistical analysis, the contents of both A and B were cleared by the manufacturer. A was omega-3 and B was the placebo after the clarification was made.

The pearls were used for 3 consecutive months. In the first month, two pearls were prescribed on a one per day basis on a single dose, for a duration of 30 days. The next 2 months pearls were prescribed for just 8 days before and 2 days after the onset of menstruation.[10] A written informed consent was obtained from all participants and review board award was given to the study.

The number of women who received the questionnaire were 184, 45 were excluded and 139 others were entered into the study and were monitored monthly by a researcher for accuracy in completing the questionnaires and medicine consumption. The sufficient amount of pearls, just for the same month, has been given to them. The number of women who have completed the study with us is 124 (Fig. 1, consort flow chart).

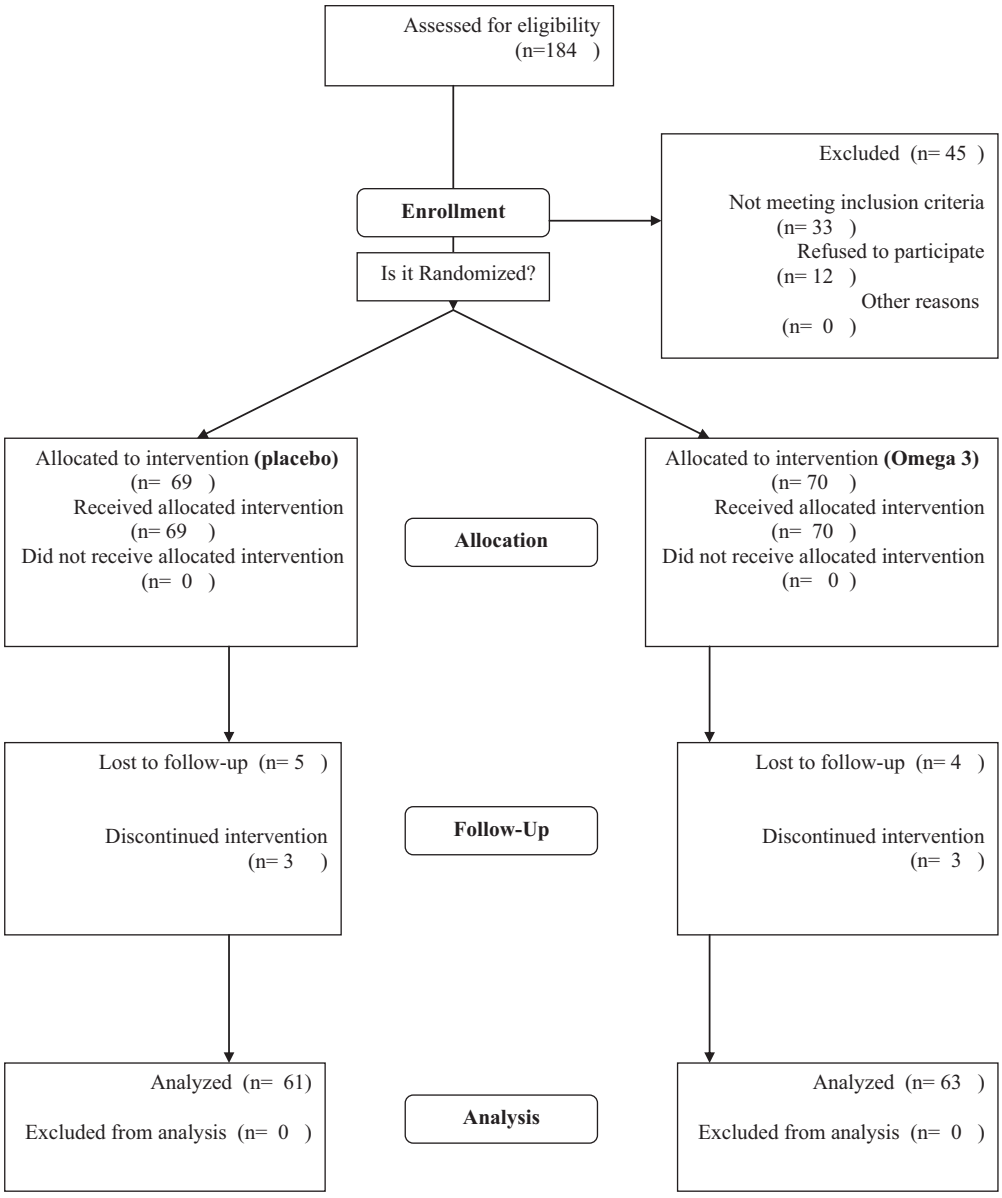

Figure 1 The consort E-flowchart.

Table 1 Characteristics of the patients of the 2 groups.

Characteristics	Omega-3 group	Placebo group
Age (year) $m \pm SD$	31.18 ± 6.54	31.64 ± 8.37
BMI $m \pm SD$	22.03 ± 4.72	22.67 ± 3.91
Sedative use n (%)	56 (93.3%)	57 (95%)

Before entering the study and after 45 days and 90 days from intervention, the severity and duration of each of the symptoms were determined according to VAS and then were compared in the two groups.

Statistical analysis was performed using SPSS 11. The chi-squared test and the Student t-test were used for comparing the data.

Results

The patients of the two groups did not have any statistically significant differences before intervention, according to age, weight, BMI, educational status, sedative use during menstruation, severity and duration of symptoms (Tables 1 and 2).

After 45 days from the beginning of the agents, mean severity of depression, anxiety, low concentration and bloating in the case group were significantly lower than the in the placebo group, but only mean duration of depression and bloating were less in the case group (Table 3).

After 90 days from drug use, the mean severity of depression, anxiety, low concentration, bloating and nervousness were lower in the case group, and duration of depression, nervousness, anxiety, low concentration, bloating, headache and breast tenderness were shorter in the case group (Table 3). Mean severity of depression, nervousness and mean duration of depression, nervousness, anxiety, breast tenderness and bloating and headache were lower 90 days after drug use in comparison with day 45 (Table 4).

Sedative use on day 90 was less in the case group than placebo group (15 cases (25%) vs. 44 case (73.3%), $P = 0.001$).

Table 2 Severity and duration of each symptom in the 2 groups before intervention (reference is made to values at baseline).

Symptoms	Omega-3	Placebo
Depression		
Severity $m \pm SD$	4.43 ± 0.71	3.75 ± 0.65
Duration $m \pm SD$	6.34 ± 2.35	7.25 ± 1.42
Nervousness		
Severity $m \pm SD$	5.25 ± 0.95	5.53 ± 0.88
Duration $m \pm SD$	6.43 ± 1.21	6.12 ± 1.01
Jitteriness		
Severity $m \pm SD$	3.27 ± 0.21	3.11 ± 0.58
Duration $m \pm SD$	7.51 ± 1.89	8.81 ± 1.37
Anxiety		
Severity $m \pm SD$	4.27 ± 1.01	4.95 ± 0.93
Duration $m \pm SD$	9.91 ± 2.33	8.25 ± 3.01
Low concentration		
Severity $m \pm SD$	5.27 ± 1.21	6.33 ± 1.35
Duration $m \pm SD$	5.43 ± 1.98	6.23 ± 1.88
Social activity		
Severity $m \pm SD$	4.31 ± 0.65	4.75 ± 0.78
Duration $m \pm SD$	3.12 ± 0.65	3.24 ± 0.35
Breast tenderness		
Severity $m \pm SD$	7.02 ± 2.32	6.35 ± 1.91
Duration $m \pm SD$	8.21 ± 3.01	8.99 ± 1.2
Bloating		
Severity $m \pm SD$	2.49 ± 0.13	3.11 ± 0.21
Duration $m \pm SD$	7.75 ± 2.47	8.35 ± 1.78
Headache		
Severity $m \pm SD$	6.11 ± 2.27	6.79 ± 2.35
Duration $m \pm SD$	4.32 ± 2.06	4.25 ± 2.61
Oedema		
Severity $m \pm SD$	2.02 ± 0.11	1.93 ± 0.17
Duration $m \pm SD$	2.05 ± 0.01	2.11 ± 0.03

Table 3 Severity of symptoms 45 and 90 days after study in the groups.

Symptoms	Severity of symptoms (day 45)		Severity of symptoms (day 90)	
	Omega-3 group Mean (SD)	Placebo group Mean (SD)	Omega-3 group Mean (SD)	Placebo group Mean (SD)
Depression שיפור מהיר בדיכאון	1.85 ± 0.73	3.72 ± 0.65	0.95 ± 0.73	3.43 ± 0.65
Nervousness שיפור מושהה בעצבנות	5.12 ± 0.93	5.25 ± 0.86	2.15 ± 0.93	6.09 ± 0.86
Jitteriness שיפור מושהה ברעד	3.17 ± 0.21	3.11 ± 0.58	1.43 ± 0.21	3.15 ± 0.58
Anxiety שיפור מהיר בחרדה	1.53 ± 1.04	4.07 ± 0.91	0.79 ± 1.04	3.89 ± 0.91
Low concentration	2.49 ± 1.26	שיפור מהיר בריכוז 5.73 ± 1.34	1.48 ± 1.26	5.63 ± 1.34
Loss of social activity	4.25 ± 0.62	4.07 ± 0.76	4.15 ± 0.63	4.17 ± 0.76
Breast tenderness	6.33 ± 2.31	6.25 ± 1.94	5.33 ± 2.31	6.05 ± 1.94
Bloating שיפור מהיר בנפיחות	0.95 ± 0.15	2.31 ± 0.19	0.74 ± 0.15	2.41 ± 0.19
Headache שיפור מושהה בכאבי ראש	5.89 ± 1.15	6.36 ± 2.07	5.79 ± 1.15	6.47 ± 2.07
Oedema	2.01 ± 0.11	1.85 ± 0.17	1.96 ± 0.11	1.89 ± 0.17

Table 4 Duration of symptoms 45 and 90 days after study in the groups.

Symptoms קיצור ניכר של משך הסימפטומים של רוב המדדים	Duration of symptoms (day 45)		Duration of symptoms (day 90)	
	Omega-3 group Mean (SD)	Placebo group Mean (SD)	Omega-3 group Mean (SD)	Placebo group Mean (SD)
Depression	4.25 ± 1.02	7.21 ± 1.32	2.12 ± 0.25	7.46 ± 0.02
Nervousness	5.46 ± 0.17	6.02 ± 0.25	2.04 ± 0.39	6.33 ± 1.45
Jitteriness	7.41 ± 2.02	7.88 ± 1.95	7.41 ± 1.32	7.63 ± 1.08
Anxiety	9.81 ± 1.43	8.23 ± 2.12	4.45 ± 1.02	8.23 ± 1.94
Low concentration	4.72 ± 1.05	5.29 ± 0.95	2.16 ± 0.26	5.55 ± 1.02
Loss of social activity	2.18 ± 0.42	2.64 ± 0.39	2.28 ± 0.83	2.35 ± 0.74
Breast tenderness	7.41 ± 1.46	7.90 ± 1.93	4.35 ± 1.31	7.85 ± 2.08
Bloating	5.53 ± 2.27	8.33 ± 1.04	3.32 ± 1.01	8.38 ± 2.32
Headache	4.02 ± 1.33	4.21 ± 1.09	2.12 ± 0.94	4.28 ± 1.58
Oedema	1.12 ± 0.23	1.15 ± 0.21	1.25 ± 0.22	1.15 ± 0.27

Discussion

In the present study the mean severity of depression, anxiety, low concentration and bloating and the duration of bloating and depression, on day 45, were lower in the omega-3 group, which may show its greater effect on mood symptoms over a short duration (time). With more prolonged use, (i.e., for 90 days), in addition to the above-mentioned symptoms, severity and duration of nervousness and duration of low concentration, headache and breast tenderness decreased. It appears that longer use is more effective for these specific symptoms. The women with a history of any psychologic disorders and any stressful events were excluded at the present study; therefore, just low-risk women were studied.

In a study by Collins et al.[7] on 27 women suffering from PMS, omega-3 fatty acids did not have any effects on the symptoms of the patients, and again, in another study by Cerin et al.[11] on some biochemical agents in women with PMS, omega-3 fatty acids could not change these factors. The sample size of this study was smaller than the present study.

Another study[12] showed no relationship between omega-3 fatty acid or fish oil consumption and depressive mood, or major depression or suicidal feelings, but this study has evaluated the low ordinary amounts of omega-3 fatty acids in diet, which is only about 2.2 g per day.

Another study[13] used higher amounts (about 9.6 g per day) and found an effective influence on bipolar disorders. In study[14] 1 g of fish oil that could release 180 mg DHA per day had protective effects on the brain.

One study[15] proposed omega-3 fatty acids as a safe and effective treatment for moderate personality disorders as a monotherapy, in women.

With regard to these controversies on the effects of omega-3 fatty acids, the present study has been conducted in order to find its probable effect on PMS symptoms.

In a study by Li,[16] 68 different studies were evaluated on how omega-3 fatty acids affected various disorders. It was found that they had good results on schizophrenia and other psychiatric disorders as well as depression.

Another study[17] concluded that it is important to continue studying the effects of omega-3 fatty acids on mood disorders and anxiety. At the same time, Rogers et al.[18] could find no significant difference between placebo and omega-3 fatty acids on the mood of patients with mild to moderate depression; thus, they concluded that the effect of omega-3 fatty acids is low.

Unfortunately, there are not many studies on the effect of omega-3 fatty acids on PMS, and to the best of our knowledge, it is the first study on this subject.

With respect to these different studies, and regarding different results, and paucity of studies concerning the effects of omega-3 fatty acids on PMS, this research team suggests the necessity of further research in order to understand omega-3's effects and better clarification on this subject.

Conflict of interest statement

There was no conflict of interest.

References

1. Speroff L, Fritz MA. *Clinical gynecologic endocrinology and infertility*. 8th ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2011. pp. 573—80.
2. Cohen LS, Soares CN, Otto MW, Sweeney BLT, Liberman RF, Harlow BL. Prevalence and predictors of premenstrual women. The Harvard study of mood and cycles. *Journal of Affective Disorders* 2002;**70**:125.
3. Kashanian M, Mazinani R, Jalalmanesh S. Pyridoxine (Vitamin B6) therapy for premenstrual syndrome. *International Journal of Gynaecology and Obstetrics* 2007;**96**(1):43—4.
4. Johnson SR. Premenstrual syndrome, Premenstrual Dysphoric Disorder, and beyond: a clinical primer for practitioners. *Obstetrics and Gynecology* 2004;**104**:845—59.
5. Kidd PM. Omega-3 DHA and EPA for cognition, behavior, and mood: clinical findings and structural—functional synergies with cell membrane phospholipids. *Alternative Medicine Review* 2007;**12**(3):207—27.
6. Berek JS. *Berek & Novak's gynecology*. 14th ed. Philadelphia, PA, 19106 USA: Lippincott Williams & Wilkins; 2007. pp. 406—8.
7. Collins A, Cerin A, Coleman G, Landgren BM. Essential fatty acids in the treatment of premenstrual syndrome. *Obstetrics and Gynecology* 1993;**81**(1):93—8.

8. Fugh- Berman A, Kronenberg F. Complementary and alternative medicine (CAM) in reproductive age women: a review of randomized controlled trials. *Reproductive Toxicology* 2003;**5503**:1—16.
9. Dell DL, Svec C. *The PMDD phenomenon*. New York, NY: Contemporary Books, MC Graw-Hill; 2003.
10. Sampalis F, Bunea R, Pelland MF, Kowalski O, Duguet N, Dupuis S. Evaluation of the effects of Neptune Krill Oil on the management of premenstrual syndrome and dysmenorrhea. *Alternative Medicine Review* 2003;**8**(May (2)):171—9.
11. Cerin A, Collins A, Landgren BM, Eneroth P. Hormonal and biochemical profiles of premenstrual syndrome. Treatment with essential fatty acids. *Acta Obstetricia et Gynecologica Scandinavica* 1993;**72**(5):337—43.
12. Hakkarainen R, Partonen T, Haukka J, Virtame J, Albanes D, Lonnqvist J. Is low dietary intake of Omega-3 fatty acids associated with depression? *American Journal of Psychiatry* 2004;**161**:567—9.
13. Stoll AL, Serverus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, et al. Omega-3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Archives of General Psychiatry* 1999;**56**:407—12.
14. Johnson EJ, Schaefer EJ. Potential role of dietary n-3 fatty acids in the prevention of dementia and macular degeneration. *American Journal of Clinical Nutrition* 2006;**83**(suppl.): 1494s—8s.
15. Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of woman with borderline personality disorders: a double-blind, placebo controlled pilot study. *American Journal of Psychiatry* 2003;**160**:167—9.
16. Li D. Omega-3 fatty acids and non-communicable diseases. *Chinese Medical Journal* 2003;**116**(3):453—8.
17. Ross BM, Sequin J, Sieswerda LE. Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? *Lipids in Health and Disease* 2007;**18**(September):6—21.
18. Rogers PJ, Appleton KM, Kessler D, Peters TJ, Gunell D, Hayward RC, et al. No effect of n-3 long chain Polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomized controlled trial. *British Journal of Nutrition* 2008;**99**(2):421—31.