

Omega-3 Supplementation and Prevention of Preterm Delivery

-a systematic review

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Abstract

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Background: To be born prematurely is associated with higher mortality and morbidity and preterm birth (PTB) is a problem world wide. It is defined by parturition before 37 completed weeks of gestation. There is a suggested association between omega-3 (n-3) fatty acids and gestational length and previous studies including women with low risk of preterm delivery (PD) have shown a decreased risk when supplemented with n-3 capsules. Whether this is applicable to pregnant women with high risk of PD is not clear since the scientific evidence regarding these women is limited.

Objective: The aim of this systematic review was to evaluate the evidence whether n-3 supplementation may reduce the risk of PD in women with high risk pregnancies compared to women receiving placebo.

Search strategy: The literature search was carried out in the databases PubMed and Scopus. MeSH-terms and free-text search words of relevance for the research question were used.

Selection criteria: The inclusion criteria were: randomised controlled trials, human studies, articles written in English and stating PD, PTB or gestational age as a primary or secondary outcome. The interventions were required to include only women with high risk pregnancies receiving long chain n-3 supplements. Studies including women with multiple pregnancies were excluded. Moreover, "fortification of foodstuffs" and "intervention starting after onset of third trimester" were also selected as exclusion criteria.

Data collection and analysis: Three articles that matched the inclusion criteria were identified and reviewed by three authors individually using a template from The Swedish Council on Health Technology Assessment. The combined strength of evidence for the three articles was set using the GRADE system.

Main results: The main finding of this systematic review was that there is moderate evidence (+ + +) that n-3 supplementation does not have an effect on reducing the risk of PTB in women with high risk pregnancies.

Conclusions: Supplementation of n-3 can at present not be recommended to women with high risk pregnancies as a tool to prevent PTB in the western world. However, it can not be ruled out that there may be other reasons for recommending n-3 supplementation during pregnancy.

Sammanfattning

Titel:	Omega-3 Supplementering och Prevention av Prematur Födsel - en systematisk översiktsartikel
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Bakgrund: Att födas för tidigt associeras med högre mortalitet och morbiditet och förtidsbörd är ett globalt problem. Det definieras som födsel innan 37 fullgångna graviditetsveckor. Tidigare studier gjorda på kvinnor med låg risk för att föda för tidigt har visat en minskad risk för förtidsbörd när de supplementeras med omega-3 fettsyror (n-3) och det finns ett möjligt samband mellan n-3 och graviditetslängd. Huruvida detta gäller för kvinnor med hög risk för att föda för tidigt är oklart då det vetenskapliga underlaget gällande dessa kvinnor är begränsat.

Syfte: Syftet med denna systematiska översiktsartikel var att undersöka huruvida n-3 supplementering kan minska risken för prematur födsel bland kvinnor med hög-riskgraviditeter jämfört med kvinnor som får placebo.

Sökväg: Litteratursökningen gjordes i databaserna PubMed och Scopus. MeSH-termer och fria sökord som var relevanta för frågeställningen användes.

Urvalskriterier: Inklusionskriterierna var: randomiserade kontrollerade studier, human studier och artiklar skrivna på engelska som angivit förtidsbörd, prematur födsel eller graviditetslängd som primärt eller sekundärt utfallsmått. Att interventionerna utfördes på kvinnor med hög risk för prematur födsel som fick långkedjiga n-3 supplement var också ett krav. Studier gjorda på kvinnor med flerbarnsbörd exkluderades, liksom studier där interventionen bestod av n-3 berikade livsmedel eller startade efter att tredje trimestern hade påbörjats.

Datainsamling och analys: Tre artiklar som uppfyllde inklusionskriterierna identifierades och granskades av tre av varandra oberoende författare. En mall från Statens Beredning för medicinsk Utvärdering användes. Den sammanvägda evidensstyrkan för de tre artiklarna bedömdes enligt GRADE-systemet.

Resultat: Denna systematiska översiktsartikels huvudsakliga resultat var att det finns måttlig evidens (+ + +) för att n-3 supplementering inte minskar risken för prematur födsel hos kvinnor med hög- riskgraviditeter.

Slutsats: I nuläget finns det inte belägg att rekommendera n-3 supplementering till kvinnor med hög-riskgraviditeter för att minska risken för prematur födsel i västvärlden. Det går dock inte att utesluta andra skäl till rekommendation av n-3 supplementering under graviditet.

Abbreviations and explanations

17P =	17 α -hydroxyprogesterone caproate
BMI =	Body Mass Index
CI =	Confidence Intervals
DHA =	Docosahexaenoic acid
E% =	Percent of total energy intake
EFSA =	European Food Safety Authority
EPA =	Eicosapentaenoic acid
IUGR=	Intra Uterine Growth Retardation
kcal=	kilocalories
LC =	Long Chain
n-3 =	Omega-3
n-6 =	Omega-6
OR =	Odds Ratio
PD =	Preterm Delivery
PG =	Prostaglandins
PIH =	Pregnancy-Induced Hypertension
PTB =	Preterm Birth
PUFA =	Polyunsaturated Fatty Acids
RCT =	Randomised Controlled Trial
RR =	Risk Ratio
SBU =	Statens Beredning för medicinsk Utvärdering (The Swedish Council on Health Technology Assessment)
WHO =	World Health Organisation

Eicosanoides:	Biologically active signalling molecules derived from 20-carbon fatty acids
Preterm birth:	Being born before 37 completed weeks of gestation
Preterm delivery:	Giving birth before 37 completed weeks of gestation
Primigravida:	A woman pregnant for the first time
Multigravida:	A pregnant woman who has experienced one or more previous pregnancies
Multiple pregnancy:	A women carrying more than one foetus

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Introduction

Preterm birth (PTB) is defined as parturition before 37 completed weeks of gestation. Globally, it is the most common cause of death amongst infants and it is estimated that 10% of all births are preterm (1). In Sweden it is estimated that almost 5% of all singleton births and 42% of multiple births are preterm (2). Aside from higher mortality, infants born prematurely also suffer higher morbidity both in the short and longer term. Being born prematurely may cause issues with underdeveloped organs such as the lungs, eyes and gastro-intestinal tract. Cognitive impairment is also a major problem for these children (3).

There are several risk factors for giving birth before reaching full-term. A previous preterm delivery (PD) is associated with an increased risk of recurrence of PD, and other risk factors include: hypertension, maternal age, multiple pregnancies, high body mass index (BMI), smoking and socioeconomic factors (4, 5). Still, the mechanisms behind PD are not yet fully understood. One factor that deserves further investigation is the suggested association between omega-3 (n-3) and length of gestation. For example, an epidemiologic study comparing birth data from the Faroe islands and Denmark showed a longer pregnancy duration in the Faroese population which correlated with a higher fish intake (6).

Long chain (LC) omega-3 and omega-6 (n-6) fatty acids are polyunsaturated and essential to human beings as we cannot synthesize them ourselves. They are therefore needed as a part of a balanced diet. Sources of n-3 fatty acids include oily fish, some types of algae, walnuts and rapeseed oil, although only the marine sources i.e. oily fish and algae contain LC n-3 (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)). Fatty acids from the n-6 family can be found in vegetable oils and to some extent in meat, dairy products and eggs (7).

In Sweden the recommended dietary intake of n-3 fatty acids is >1E% (8), which is equal to 2.2 g for a person with a daily intake of 2,000 kcal. Moreover, it is stated in the Nordic Nutrition Recommendations that an intake of 200-250 mg EPA and DHA is associated with positive health effects (8). Both the World Health Organisation (WHO) and the European Food Safety Authority (EFSA) also recommend an intake of 250 mg EPA and DHA per day (9). The average Swedish intake of n-3 fatty acids is estimated to be 2.7 g/day (10), similar between the genders, which exceeds the recommendations for both men and women.

In a systematic analysis by Micha et al (11) it was found that 45 out of 187 countries had an adequate average intake of marine sources of omega-3, i.e. >250 mg, whereas 2/3 of the countries had a very low mean consumption: <100 mg/day. The lowest intakes were generally found in countries in Sub-Saharan Africa, North Africa, the Middle East and some Asian regions. The same systematic analysis concluded that the global mean intake of DHA and EPA is 163 mg/day although the national variation ranges from 5 mg - 3886 mg/day (11).

LC n-3 fatty acids promote normal growth and overall health and also play a vital role in the development of the neurological system and vision (12). In the beginning of the third trimester the foetus' brain starts to grow rapidly and 30-45 mg of DHA is accumulated in the central nervous system daily (13). Omega-3 and omega-6 share the same metabolic pathway and compete for the same enzymes. Historically the dietary intake ratio between n-6 and n-3 fatty acids has been as low as 1-2:1 in western diets, whereas the current western diet has a ratio of approximately 20-30:1 (14). LC polyunsaturated fatty acids (PUFA) of the n-3 and n-6 families are precursors to prostaglandins

(PG), which are a type of eicosanoides. Prostaglandins are hormone-like substances with many physiological functions, e.g. blood pressure regulation, muscle tonus, and they also play a role in the onset of parturition (15). It is believed that an increased intake of n-3 fatty acids reduces the PGs derived from n-6 fatty acids which are vasoconstricting and may induce labour (16).

As previously mentioned, a history of PD increases the recurrence risk. Today different pharmacological prophylactic treatments such as 17 α -hydroxyprogesterone caproate (17P) can be given to women with high risk pregnancies (16). 17P is a synthetic version of the hormone progesterone and is believed to reduce the risk of PD by contributing to a lower activity of the uterine smooth muscles (17). As it stands, n-3 is not currently used as a prophylactic treatment for PD. However, it is a topic that is under research. A systematic review including women with low risk pregnancies has shown a positive effect of n-3 supplementation or fortification on pregnancy duration and a decreased risk of PD (18). The doses used in the systematic review ranged from 133 mg of DHA to 2.7 g EPA + DHA. One of the included studies was conducted using fortification of eggs, and showed a significant reduction in PD (19). Another study, not included in the systematic review, administering fortified milk powder, containing DHA amongst other nutrients, did not show any significant results for the outcome measure gestational age. A tendency was seen towards longer gestation but the power was estimated to be too low as this was a secondary outcome (20). Most studies that are conducted include only women with low risk of PD and the clinical relevance of further lowering the risk in this population can be discussed.

Problem

PTB is associated with higher mortality and morbidity and is a problem worldwide. A previous PD is the greatest risk factor for parturition before 37 weeks. The scientific evidence regarding women with high risk pregnancies and n-3 supplementation is limited and not up to date, although it could be argued that these women would potentially benefit the most from such intervention. Since a positive effect has been found in women with low risk pregnancies, it is likely that women with high risk pregnancies could also benefit from this prophylactic treatment and therefore an updated systematic review is needed.

Aim

The aim of this systematic review was to evaluate the evidence whether n-3 supplementation could reduce the risk of PD in women with high risk pregnancies.

Research question

Does omega-3 supplementation during pregnancy, compared with placebo, reduce the risk of preterm delivery in women with high risk pregnancies?

Method

This systematic review summarises the literature published until January 2015 regarding omega-3 supplementation in high risk pregnancies and the reduction of risk of PD.

Inclusion and exclusion criteria

When searching for scientific articles the following criteria were used during the data collection:

Inclusion criteria

- Randomized controlled trial (RCT)
- Articles written in English
- Preterm birth, preterm delivery or gestational age stated as a primary or secondary outcome
- LC n-3 (EPA and DHA) supplementation during pregnancy
- Women with high risk pregnancies
- Human studies

Exclusion criteria

- Women with multiple pregnancy
- Fortification of foodstuffs
- Intervention starting after onset of third trimester (gestation week 29)

Collection of data

A systematic literature search in two databases (PubMed and Scopus) was conducted by all three authors. MeSH-terms and free-text search words in several combinations were used during the search in PubMed to ensure that no relevant articles were missed. The search strategy in PubMed included the use of filters to exclude articles that were not written in English, of a different study design than RCT and to include only human studies. The search function was different in Scopus which made it more difficult to limit and define the searches. Text words relevant to the research question were used. Search functions “AND”, “OR” and “AND NOT” were used in both databases to extract relevant articles. Titles and, if necessary, abstracts were read and articles were either excluded or included for further analysis depending on the relevance for the research question. In total 32 articles were identified by this method. Dates and search words are shown in Table 1.

Table 1. Literature search

Search	Database	Date	Search words	Limitations	Matches found	Chosen articles	References
1	Pubmed	27/01/15	Fatty acids, omega-3 OR fish oils AND obstetric labor, premature	English, RCT, human	13	9	(19, 21-28)
2	Pubmed	27/01/15	Fatty acids, omega-3 OR fish oils AND pregnancy duration	English, RCT, human	8	6[3]	(19, 22, 27, 29-31)
3	Pubmed	27/01/15	Fatty acids, omega-3 OR fish oils AND gestational duration	English, RCT, human	5	3[3]	(19, 22, 27)
4	Pubmed	27/01/15	Fatty acids, omega-3 OR fish oils AND gestational length	English, RCT, human	17	7[3]	(19, 22, 28, 32-35)
5	Pubmed	27/01/15	Fatty acids, omega-3 OR fish oils AND pregnancy length	English, RCT, human	13	10[8]	(19, 22, 28, 30, 32-37)
6	Scopus	28/01/15	Omega-3 AND supplement AND preterm birth OR premature birth OR pregnancy length OR pregnancy duration OR gestational length OR gestational duration OR preterm labor OR premature labor AND NOT breastfeeding AND NOT nursing AND NOT Rat	English, article	17	6 [6]	(22, 27-30, 33)
7	Scopus	28/01/15	Omega-3 OR fish-oils AND pregnancy AND premature OR preterm OR birth OR duration AND NOT rat	English, article	275	25[11]	(22, 24-30, 33-35, 38-51)

[] = duplicates

A review of the methods of the 32 articles was performed to evaluate the correspondence between the articles and the inclusion criteria. This resulted in three included articles by Harper et al (2010), Olsen et al (2000), and Onwude et al (1995) (24, 26, 31). Snowballing was performed on the three included articles and a systematic review on the effect of PUFA intake during pregnancy (42), which led to the identification of a fourth article (52). However it was excluded due to poor accordance with the inclusion criteria. In the excluded article, gestational length was measured, although the main focus was pregnancy induced hypertension (PIH) and intra-uterine growth retardation (IUGR) and neither PTB or gestational age were stated as a primary or secondary outcome. See flowchart (Figure 1). Reasons for the exclusion of articles are presented in Appendix 1.

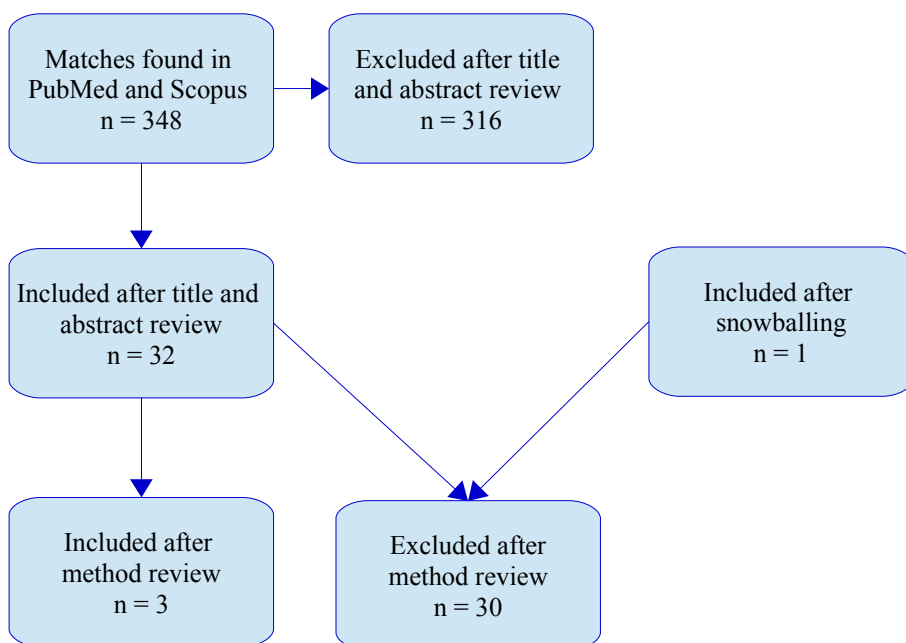


Figure 1. Flowchart over literature selection

Processing of data

The three included articles were read, analysed and graded separately by the three authors. The outcome measure reviewed was PD i.e. parturition before 37 completed weeks of gestation. Using a template from The Swedish Council on Health Technology Assessment (SBU) (53), the authors individually evaluated the risk of selection bias, performance bias, detection bias, attrition, reporting bias and other considerations such as conflicts of interest, resulting in a combined score for each article: low, moderate or high risk of bias. Subsequently the grading was compared and consensus was reached regarding a score for each article. Grading of evidence for the three articles was performed by the three authors together by using a modified GRADE-template from the University of Gothenburg.

GRADE is an acronym for “the Grading of Recommendations Assessment, Development and Evaluation” and is a system for grading quality and strength of evidence in health care (54). The score system within GRADE rates evidence and quality as High (+++), Moderate (+++), Low (++) or Very Low (+).

Results

The included articles are summarised in Table 2 and subsequently presented individually in text. A compiled judgment of the strength of evidence can be found under “Grading of evidence”.

Table 2. Description of studies.

Author Year Country	Study design	Population (n/drop-outs)	Intervention Control	Preterm delivery as a primary/ secondary outcome measure	Delivery < 37 weeks	Compliance Measurement of compliance	Quality of study
Harper, M., et al. 2010 United States of America	RCT 13 multicentre trials	Pregnant women with Previous PD on 17 α -hydroxy- progesterone treatment. n = 852 (no drop outs)	Intervention: 4 capsules daily containing a total of 2 g n-3 fatty acids, of which 1.2 g EPA and 0.8 g DHA. Control: 4 matching capsules containing inert mineral oil	Primary	Intervention group: 37.8% Control group: 41.6% (RR 0.91, 95% CI 0.77 to 1.07)	The compliance rate was 85.1% in the fish oil group and 84.8% in the placebo group Measurement method: Capsule counting	High
Olsen, S. F., et al. 2000. Denmark	RCT 6 multicentre trials	Pregnant women with previous PD or PIH or IUGR. n = 898 (57 drop outs)	Intervention: 4 capsules (Pikaso) daily containing a total of 2.7 g n-3 fatty acids, of which 1.3 g EPA and 0.9 g DHA. Control: 4 capsules containing olive oil	Primary	Intervention group: 10.6% Control group: 15.2% * (OR 0.67, 95% CI 0.41 to 1.07).	80.3% in the fish oil group and 78.3% in the olive oil group took their prescribed capsules Measurement method: Compliance forms. 98% answering frequency.	Moderate- high
Onwude, J. L., et al. 1995. United Kingdom.	RCT	Pregnant women with a history of at least one small baby, a history of PIH, a history of unexplained stillbirth or abnormal uterine artery Doppler blood flow. n = 233 (1 drop out)	Intervention: 9 capsules (MaxEpa) daily containing a total of 2.7 g n-3 fatty acids of which 1.62 g EPA and 1.08 g DHA. Control: 9 matching air-filled capsules daily	Secondary	Intervention group: 18.6% Control group: 16%**	50% in the fish oil group and 57% in the placebo group took >70% of prescribed capsules Measurement method: Capsule counting	Low- moderate

*Data presented after eliminating elective deliveries.

**Confidence intervals not shown.

Description of studies

Harper et al, 2010.

Omega-3 fatty acid supplementation to prevent recurrent preterm birth: A randomized controlled trial (24).

This double-blinded RCT was carried out in 13 centres in the USA. Overall 852 pregnant women with a previous singleton spontaneous PD were included and none was lost to follow up. The women were randomised to either the intervention group or the placebo group. Both groups received a weekly intramuscular injection of 17P caproate (250 mg). Additionally the intervention group was supplemented with n-3 capsules, containing 1.2g EPA and 0.8g DHA, whilst the control group received matching capsules filled with inert mineral oil, to be taken daily in both cases.

All women were included between 16-22 weeks of gestation and capsules were given until parturition or 37 completed weeks of gestation, whichever occurred first. Gestational age was determined using ultrasound examination and information on the last menstrual period. The study objective was to evaluate the effect of n-3 supplementation on the recurrence risk for PD in women already receiving 17P caproate. The primary outcome stated was delivery before 37 completed weeks of gestation. Compliance was measured by capsule count and the mean compliance rate for the n-3 group was 85.1% and 84.8% in the placebo group.

Results: The gestational length was on average two days longer in the intervention group. However, the difference was not significant ($P=0.26$). Nor was there a significant difference in the risk of PD (relative risk [RR] 0.91, 95% confidence interval [CI] 0.77 to 1.07).

Quality assessment: The study quality was rated as high. The participants were randomised through the simple urn method and the baseline characteristics for the two groups were similar. Considering that the study was double-blinded, none was lost to follow up and compliance was deemed to be satisfactory, the risk of bias was judged to be low.

Olsen et al, 2000.

Randomised clinical trials of fish oil supplementation in high risk pregnancies (26).

This study, consisting of six separate multicentre double-blinded RCTs, was carried out in 19 centres in Europe. The study in whole included 1619 women, distributed over six trials based on the women's medical and obstetric history. In all six trials the women were randomised to an intervention group or a control group. Trial A included 232 women with a previous PD. Trial B included 280 women with IUGR in a prior pregnancy. Trial C included 386 women who in an earlier pregnancy had experienced PIH. Trial D included 579 women carrying twins. These four trials were labelled as prophylactic. The two remaining trials, trial E and trial F, were labelled therapeutic. Trial E included 79 women with threatening pre-eclampsia and trial F included 63 women with suspected IUGR in their current pregnancies. Trial D, E and F did not match the inclusion criteria for this systematic review and therefore only the 898 women from trial A, B and C are included in this systematic review.

The intervention groups in trials A, B and C were supplemented with a daily dose of n-3 capsules containing 1.3g EPA and 0.9g DHA. The control groups were given matching capsules of olive oil. Supplementation started around gestational week 20 for all women. Gestational age was determined using ultrasound examination where possible and information on the last menstrual period when no ultrasound examination was performed. The study objective was to investigate the presupposed positive effect of n-3 intake on PD, PIH and IUGR, which were also the main outcome measures. Compliance was measured through questionnaires mailed to the women in Scandinavian and English-speaking countries. In total 57 women dropped out (6%).

Results: When elective deliveries were excluded the gestational length was on average 4.8 days (95% CI 1.96 to 7.67) longer in the group who received fish oil, but there was no significant reduction in risk of PD in the combined trials (odds ratio [OR] 0.67, CI 0.41 to 1.07). However, in trial A (women with a previous PD) the recurrence risk was significantly reduced (OR 0.54, 95% CI 0.30 to 0.98).

Quality assessment: The study quality was rated as moderate/high. The participants were randomised through restricted block-wise computer generated randomisation and the baseline characteristics were similar for the intervention and control groups in all trials. The overall risk of bias was low/moderate considering the incomplete compliance measuring method, the absence of analysis of drop-out data and inconsistency in the method used to determine gestational age.

Onwude et al, 1995.

A randomised double blind placebo controlled trial of fish oil in high risk pregnancy (31).

This double-blinded RCT was carried out in the UK. A total of 232 pregnant women were included in the study, of whom 160 were multigravida with either a history of one or more small babies, a history of proteinuric or nonproteinuric PIH or a history of unexplained stillbirth. The remaining 72 were primigravida with abnormal uterine arcuate artery Doppler blood flow at 24 weeks of gestation. One woman from the group of multigravida was lost to follow up. The women were randomised to either the intervention group or the control group. The intervention group received n-3 capsules containing 1.62 g EPA and 1.08 g DHA and the control group was given matching air-filled capsules to be taken daily.

Supplementation started around gestational week 24 and was continued until gestational week 38. Gestational age was determined using ultrasound examination. The objective of the study was to examine the potential beneficial effect of n-3 fatty acid supplementation during pregnancy. Main outcome measures were occurrence of proteinuric or nonproteinuric PIH or birth weight < 3rd centile. Gestational age at delivery was a secondary outcome. Compliance was measured through capsule counting, 50% of the participants in the intervention group and 43% in the control group took > 70% of their supplied capsules.

Results: There was no significant difference in any of the outcome measures. Mean gestation in weeks was 38.1 in both the intervention and control group (95% CI between the groups was -0.07 to 0.06). Delivery before 37 completed weeks of gestation occurred in 18.6% of the pregnancies in the intervention group and 16% of the pregnancies in the control group. However, no CI or P-values were presented for this outcome.

Quality assessment: The study quality was rated as low/moderate. The randomisation was computer-generated and carried out through the principle of third-party randomisation and the baseline characteristics were sufficiently similar. The principal issue of the study was the poor compliance. Moreover, the absence of an appropriate statistical presentation of the outcome measure of interest for this systematic review contributed to the overall risk of bias being judged to be moderate/high.

Grading of evidence

The GRADE analysis of the outcome measure PD is presented in Table 3. The aggregated strength of evidence was determined to be moderate (+ + +). Some limitations concerning the internal validity were agreed upon due to the unsatisfactory compliance in Onwude et al (31), and the unsuitable method of measuring compliance in Olsen et al (26). Additionally, the difficulty in blinding the marine taste of the n-3 capsules contributed to the assessment of the internal validity. No limitations were found regarding homogeneity: none of the studies found a significant positive effect of the intervention although two of the studies showed a positive trend in the reduction of risk of PD. Moreover, Olsen et al (26) found a difference (p=0.05) when Trial A, including the women with a previous PD and thus being at the highest risk, was analysed separately. Some limitations were also seen in terms of precision due to the absence of confidence intervals or P-values in Onwude et al (31) for the outcome measures of interest in this systematic review. There were no limitations observed as to the external validity or risk of publication bias.

Table 3. Strength of evidence.

Outcome measure	Preterm delivery
Number of studies	3
Study design – internal validity	Some limitations
Homogeneity	No limitations
Study population – external validity	No limitations
Precision	Some limitations
Publication bias	No limitations
Strength of evidence	Moderate (+ + +)

Discussion

The main finding of this systematic review is that there is moderate evidence (+ + +) that n-3 supplementation does not have an effect on reducing the risk of PD in women with high risk pregnancies. There was no difference in parturition before 37 weeks of gestation amongst the women who received n-3 capsules and those who did not. However, a trend of a small increase in gestational length was observed.

Method discussion

The literature search was conducted in the databases PubMed and Scopus. Performing a search in these databases requires some skill due to the difficulty of limiting the search without missing relevant articles. The matter is further complicated by the fact that the databases are not designed in the same way and therefore function differently. To minimise the risk of not identifying all articles matching the inclusion criteria, several searches with different search words were carried out which can be seen as a strength of this article. Another strength is that three authors independently reviewed the three included articles, using standardised templates (53).

Criteria for inclusion and exclusion were determined to enable an answer to the research question. PTB, PD or gestational age stated as a primary or secondary outcome were decided upon to ensure that the study in question was designed to investigate the outcome of interest for this systematic review. If an outcome is presented without being stated as primary or secondary, there may be a risk of type II error due to the sample size not being calculated for observing a significant difference in the outcome of interest. Trials including n-3 fortified foodstuffs instead of supplementation through capsules were excluded due to the possible confounding effects of other components in the food.

To keep the intervention and study populations homogenous, exclusion criteria were set regarding interventions including multiple pregnancies and onset of supplementation. Trials including women with multiple pregnancies were excluded since women carrying more than one foetus run a considerably higher risk of PD than other women (55). Whether n-3 supplementation reduces the risk of PD in women with multiple pregnancies is an interesting and important question. However, this population requires a separate systematic review. Furthermore, it was decided that supplementation of n-3 should commence before the women entered the third trimester considering the hypothetical increased requirement during this period (56).

The relevance of choosing “intervention starting after onset of third trimester (gestation week 29)” as an exclusion criteria can be discussed. A rapid effect of n-3 supplementation on gestational length has been proposed (18), but the scientific evidence supporting this theory is limited and most studies commence supplementation when the women are in the second trimester. Therefore, only trials with this design were included to keep the interventions comparable.

Result discussion

'High risk pregnancies' is a term used in the three included articles describing the participating women, although there is no consistent definition. All trials in this systematic review included women with an increased risk of PD, but the studies all had different inclusion criteria and the underlying risk factors differed in the women. One of the studies only included women with a previous PD (24), whereas the other two included women with various risk factors (26, 31). A significant difference between intervention and control women was observed in the study by Olsen et al when Trial A (including only women with a previous PD) was analysed independently, which may be an indication for the importance of separating the different risk factors in future studies. The absence of significant results in the study conducted by Harper et al, which also only included women with a previous PD, can possibly be explained by the fact that they were already undergoing treatment to prevent recurrence. An additional risk reduction of n-3 supplementation on PD might not be possible in women already receiving 17P. Since a slight tendency towards a reduction in risk of PD was seen in the studies by Harper et al and Olsen et al, another possible reason for the absence of significant results is that the sample sizes might have been too small to reach power.

A major difficulty in conducting RCTs involving supplementation with n-3 capsules is the complexity of blinding. All studies in this systematic review were designed to be double-blinded, however, in two of the studies it was reported that many of the women in the intervention groups correctly guessed that they were allocated to the fish-oil group. In the article by Olsen et al, the authors even state that the capsules were not identical in taste. Some studies attempt to flavour both the placebo and fish-oil capsules with other flavours e.g. orange (22), although a potentially better solution would be to not attempt to mask the fish taste, but instead add fish flavour to the placebo capsules. That way, participants in the control groups would be more likely to believe that they are allocated to the intervention group.

A prerequisite for obtaining a possible effect of the intervention in a RCT is that the participants follow given instructions. It is very difficult to draw conclusions from studies where compliance is low due to the fact that the fundamental idea of an RCT is that there is one intervention group and one control group and that they follow two different regimes. In the study by Onwude et al compliance was poor, which is the main reason for its assessed low/moderate quality. There is a possibility that an effect of the n-3 supplementation could have been observed if the percentage of capsules taken had been higher in the intervention group. It may also be possible that a significant difference could have been observed if the doses n-3 in the included studies had been higher. Similar doses has shown a reduction of PD in low risk pregnancies (18) and it could be argued that for women with high risk pregnancies those doses are not sufficient.

The content of the placebo capsules is a possible confounding factor. As discussed in the article by Olsen et al, it is not possible to know for certain that olive oil is completely inert, as it contains n-6 fatty acids. If n-6 in fact has an adverse effect in preventing PD, the n-3 supplementation would appear more beneficial in studies where the placebo capsules contain n-6 fatty acids. Since the placebo consisted of olive oil capsules in the only trial with a significant difference (Trial A, Olsen et al), there is a slight possibility that this difference is due to an increased risk of PD in the placebo group, rather than a decreased risk in the intervention group.

Another potential confounder is the women's food intake in general and particularly their fish intake. Regardless if a significant difference is obtained or not, this might be explained by variation

between the groups in food intake. Only one of the included studies in this systematic review measured fish intake at baseline to ensure similarity between the groups (24). In the studies that did not measure fish intake, a non-significant difference might be caused by a higher intake of fish in the control group. As a participant in a study investigating positive effects of n-3, it is conceivable that, consciously or subconsciously, one might be inclined to eat more fish than usual.

Omega-3 in a local and global perspective

Since all three of the studies included in this systematic review were carried out in the developed world where n-3 intake is generally sufficient, and none of the articles reported the women's n-3 intake, it is possible that n-3 supplementation has no effect on women with an already adequate n-3 intake. As previously mentioned the average Swedish intake of n-3 fatty acids exceeds the recommendation of >1E%. However, it is important to keep in mind that it is in fact an average, therefore being an inadequate measure of individual intake. It is probable that there is a great difference between the individuals with the lowest and highest intakes, and n-3 supplementation may be beneficial for women who do not meet the recommendations.

Globally, the range of n-3 intake is very wide and many people do not meet the recommendations. Hypothetically, if the whole world's population were to eat oily fish, or n-3 supplements derived from fish, in amounts meeting the recommendations, the already threatened fish population would be in even greater danger than it is today. According to Nichols et al (57) the global fish stock is so vulnerable that it might collapse as soon as 2048. It can be argued that the solution to the problem of providing the whole world with adequate amounts of LC n-3 fatty acids does not lie solely in increased fish consumption, but in alternative sources such as algae and possibly even genetically modified foods.

Conclusion

In conclusion, there is moderate evidence that n-3 supplementation has no effect on preventing PD in women with high risk pregnancies in the western world. At present, n-3 supplementation can not be recommended as a tool to prevent PD for women with a high risk. However, it is plausible that supplementation has other beneficial effects since n-3 is important in foetal development. Other reasons for recommending n-3 capsules in pregnancy can therefore not be ruled out.

If further research is carried out on this topic, it would be advisable to separate women with different risk factors since women with certain risk factors, such as a previous PD as shown in the article by Olsen et al, may benefit more than women with other risk factors from supplementation with n-3. Since the three studies included in this systematic review were all carried out in the western world where n-3 intake is generally sufficient, it could be relevant to investigate if n-3 supplementation has an effect in women with high risk pregnancies in less developed parts of the world, where n-3 intake is lower (11). Measuring n-3 status and fish intake at baseline and throughout the study to identify a possible difference in outcome between women with high and low levels of n-3 would be interesting. If such a difference were to be observed, this could be helpful in setting nutritional recommendations for pregnant women in the future.

References

1. World Health Organization MoD, ; The Partnership for Maternal, Newborn and Child Health,; Save the Children, . Born too soon -The global action report on preterm birth. http://www.who.int/maternal_child_adolescent/documents/born_too_soon/en/: World Health Organization, 2012 05/02/2015.
2. Socialstyrelsen. Graviditeter, förlossningar och nyfödda barn. <http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19627/2014-12-19.pdf>; Socialstyrelsen, 2014 05/02/2015.
3. Platt MJ. Outcomes in preterm infants. *Public health*. 2014;128(5):399-403.
4. Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, et al. The preterm prediction study: Risk factors for indicated preterm births. *American Journal of Obstetrics and Gynecology*. 1998;178(3):562-7.
5. Räisänen S, Gissler M, Saari J, Kramer M, Heinonen S. Contribution of Risk Factors to Extremely, Very and Moderately Preterm Births - Register-Based Analysis of 1,390,742 Singleton Births. *PLoS ONE*. 2013;8(4):e60660.
6. Olsen SF, Joensen HD. High liveborn birth weights in the Faroes: a comparison between birth weights in the Faroes and in Denmark. *Journal of epidemiology and community health*. 1985;39(1):27-32.
7. Livsmedelsverket. Fettsyror Livsmedelsverket2013 [updated 04/12/201309/02/2015]. Available from: <http://www.slv.se/sv/grupp1/Mat-och-naring/Vad-innehaller-maten/Livsmedelsdatabasen-/Naringsammen-och-varden/Fett/Fettsyror/>.
8. Nordic Nutrition Recommendations 2012 : integrating nutrition and physical activity. Copenhagen: Nordic Council of Ministers; 2014.
9. Salem N, Jr., Eggersdorfer M. Is the world supply of omega-3 fatty acids adequate for optimal human nutrition? *Current opinion in clinical nutrition and metabolic care*. 2015;18(2):147-54.
10. Livsmedelsverket. Riksmaten – vuxna 2010–11. Livsmedels- och näringsintag bland vuxna i Sverige. 2012.
11. Micha R, Khatibzadeh S, Shi P, Fahimi S, Lim S, Andrews KG, et al. Global, regional, and national consumption levels of dietary fats and oils in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys. *BMJ (Clinical research ed)*. 2014;348:g2272.
12. Harris WS, Baack ML. Beyond building better brains: bridging the docosahexaenoic acid (DHA) gap of prematurity. *Journal of perinatology : official journal of the California Perinatal Association*. 2015;35(1):1-7.
13. Koletzko B, Cetin I, Brenna JT. Dietary fat intakes for pregnant and lactating women. *The British journal of nutrition*. 2007;98(5):873-7.
14. Simopoulos AP. Essential fatty acids in health and chronic disease. *The American journal of clinical nutrition*. 1999;70(3 Suppl):560s-9s.
15. Hansen HS, Olsen SF. Dietary (n-3)-fatty acids, prostaglandins, and prolonged gestation in humans. *Progress in clinical and biological research*. 1988;282:305-17.

16. Facchinetti F, Fazzio M, Venturini P. Polyunsaturated fatty acids and risk of preterm delivery. *Eur Rev Med Pharmacol Sci.* 2005;9(1):41-8.
17. Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *The Cochrane database of systematic reviews.* 2013;7:Cd004947.
18. Salvig JD, Lamont RF. Evidence regarding an effect of marine n-3 fatty acids on preterm birth: a systematic review and meta-analysis. *Acta obstetricia et gynecologica Scandinavica.* 2011;90(8):825-38.
19. Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. *Obstet Gynecol.* 2003;101(3):469-79.
20. Mardones F, Urrutia MT, Villarroel L, Rioseco A, Castillo O, Rozowski J, et al. Effects of a dairy product fortified with multiple micronutrients and omega-3 fatty acids on birth weight and gestation duration in pregnant Chilean women. *Public health nutrition.* 2008;11(1):30-40.
21. Caritis SN, Venkataramanan R, Thom E, Harper M, Klebanoff MA, Sorokin Y, et al. Relationship between 17-alpha hydroxyprogesterone caproate concentration and spontaneous preterm birth. *Am J Obstet Gynecol.* 2014;210(2):128.e1-6.
22. Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, et al. DHA supplementation and pregnancy outcomes. *Am J Clin Nutr.* 2013;97(4):808-15.
23. Harper M, Li L, Zhao Y, Klebanoff MA, Thorp JM, Jr., Sorokin Y, et al. Change in mononuclear leukocyte responsiveness in midpregnancy and subsequent preterm birth. *Obstet Gynecol.* 2013;121(4):805-11.
24. Harper M, Thom E, Klebanoff MA, Thorp J, Sorokin Y, Varner MW, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: A randomized controlled trial. *Obstet Gynecol.* 2010;115(2 PART 1):234-42.
25. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P, et al. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: A randomized controlled trial. *J Am Med Assoc.* 2010;304(15):1675-83.
26. Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Gluud C. Randomised clinical trials of fish oil supplementation in high risk pregnancies. *Br J Obstet Gynaecol.* 2000;107(3):382-95.
27. Olsen SF, Østerdal ML, Salvig JD, Weber T, Tabor A, Secher NJ. Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: A randomised clinical trial with fish oil. *Eur J Clin Nutr.* 2007;61(8):976-85.
28. Ramakrishnan U, Stein AD, Parra-Cabrera S, Wang M, Imhoff-Kunsch B, Juárez-Márquez S, et al. Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: Randomized, double-blind, placebo-controlled trial in Mexico. *Food Nutr Bull.* 2010;31(2 SUPPL.):S108-S16.
29. Imhoff-Kunsch B, Stein AD, Martorell R, Parra-Cabrera S, Romieu I, Ramakrishnan U. Prenatal docosahexaenoic acid supplementation and infant morbidity: Randomized controlled trial. *Pediatrics.* 2011;128(3):e505-e12.
30. Olsen SF, Sørensen JD, Secher NJ, Hedegaard M, Henriksen TB, Hansen HS, et al. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. *Lancet.* 1992;339(8800):1003-7.

31. Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. *Br J Obstet Gynaecol.* 1995;102(2):95-100.
32. Helland IB, Saugstad OD, Smith L, Saarem K, Solvoll K, Ganes T, et al. Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. *Pediatrics.* 2001;108(5):E82.
33. Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics.* 2003;111(1):e39-44.
34. Lucia Bergmann R, Bergmann KE, Haschke-Becher E, Richter R, Dudenhausen JW, Barclay D, et al. Does maternal docosahexaenoic acid supplementation during pregnancy and lactation lower BMI in late infancy? *J Perinat Med.* 2007;35(4):295-300.
35. Zhou SJ, Yelland L, McPhee AJ, Quinlivan J, Gibson RA, Makrides M. Fish-oil supplementation in pregnancy does not reduce the risk of gestational diabetes or preeclampsia. *Am J Clin Nutr.* 2012;95(6):1378-84.
36. Freeman MP, Davis M, Sinha P, Wisner KL, Hibbeln JR, Gelenberg AJ. Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. *J Affect Disord.* 2008;110(1-2):142-8.
37. Stein AD, Wang M, Martorell R, Neufeld LM, Flores-Ayala R, Rivera JA, et al. Growth to age 18 months following prenatal supplementation with docosahexaenoic acid differs by maternal gravidity in Mexico. *J Nutr.* 2011;141(2):316-20.
38. Dunstan JA, Mori TA, Barden A, Beilin LJ, Holt PG, Calder PC, et al. Effects of n-3 polyunsaturated fatty acid supplementation in pregnancy on maternal and fetal erythrocyte fatty composition. *Eur J Clin Nutr.* 2004;58(3):429-37.
39. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: A randomized, controlled trial. *J Allergy Clin Immunol.* 2003;112(6):1178-84.
40. Gould JF, Makrides M, Colombo J, Smithers LG. Randomized controlled trial of maternal omega-3 long-chain PUFA supplementation during pregnancy and early childhood development of attention, working memory, and inhibitory control. *Am J Clin Nutr.* 2014;99(4):851-9.
41. Helland IB, Saugstad OD, Saarem K, Van Houwelingen AC, Nylander G, Drevon CA. Supplementation of n-3 fatty acids during pregnancy and lactation reduces maternal plasma lipid levels and provides DHA to the infants. *J Matern-Fetal Neonatal Med.* 2006;19(7):397-406.
42. Imhoff-Kunsch B, Briggs V, Goldenberg T, Ramakrishnan U. Effect of n-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: A systematic review. *Paediatr Perinat Epidemiol.* 2012;26(SUPPL. 1):91-107.
43. Knudsen VK, Hansen HS, Østerdal ML, Mikkelsen TB, Mu H, Olsen SF. Fish oil in various doses or flax oil in pregnancy and timing of spontaneous delivery: A randomised controlled trial. *BJOG Int J Obstet Gynaecol.* 2006;113(5):536-43.
44. Malcolm CA, McCulloch DL, Montgomery C, Shepherd A, Weaver LT. Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: A double blind, prospective, randomised trial. *Arch Dis Child Fetal Neonatal Ed.* 2003;88(5):F383-F90.
45. Mulder KA, King DJ, Innis SM. Omega-3 fatty acid deficiency in infants before birth identified using a

- randomized trial of maternal DHA supplementation in pregnancy. PLoS ONE. 2014;9(1).
- 46 Olsen SF, Hansen HS, Secher NJ, Jensen B, Sandstrom B. Gestation length and birth weight in relation to intake of marine n-3 fatty acids. *BR J NUTR*. 1995;73(3):397-404.
47. Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddle R, Gibson RA, et al. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: Randomised controlled trial. *BMJ (Online)*. 2012;344(7845):14.
48. Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddle R, Gibson RA, et al. Randomized controlled trial of fish oil supplementation in pregnancy on childhood allergies. *Allergy Eur J Allergy Clin Immunol*. 2013;68(11):1370-6.
49. Pietrantoni E, Del Chierico F, Rigon G, Vernocchi P, Salvatori G, Manco M, et al. Docosahexaenoic acid supplementation during pregnancy: A potential tool to prevent membrane rupture and preterm labor. *Int J Mol Sci*. 2014;15(5):8024-36.
50. Ray JG. Fish oil supplementation reduced the recurrence of preterm delivery but not IUGR or hypertension. *Evid-based Obstet Gynecol*. 2000;2(4):95.
51. Van Houwelingen AC, Sorensen JD, Hornstra G, Simonis MMG, Boris J, Olsen SF, et al. Essential fatty acid status in neonates after fish-oil supplementation during late pregnancy. *BR J NUTR*. 1995;74(5):723-31.
52. Bulstra-Ramakers MT, Huisjes HJ, Visser GH. The effects of 3g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension. *Br J Obstet Gynaecol*. 1995;102(2):123-6.
53. Statens beredning för medicinsk utvärdering. Mall för kvalitetsgranskning av randomiserade studier 2012 [10/02/2015]. Available from: http://www.sbu.se/upload/ebm/metodbok/Mall_randomiserade_studier.pdf.
54. The Grading of Recommendations Assessment Development and Evaluation. GRADE 2014 [10/02/2015]. Available from: <http://www.gradeworkinggroup.org/>.
55. Kurdi AM, Mesleh RA, Al-Hakeem MM, Khashoggi TY, Khalifa HM. Multiple pregnancy and preterm labor. *Saudi medical journal*. 2004;25(5):632-7.
56. Larque E, Gil-Sanchez A, Prieto-Sanchez MT, Koletzko B. Omega 3 fatty acids, gestation and pregnancy outcomes. *The British journal of nutrition*. 2012;107 Suppl 2:S77-84.
57. Nichols PD, Petrie J, Singh S. Long-Chain Omega-3 Oils—An Update on Sustainable Sources. *Nutrients*. 2010;2(6):572-85.

Appendix 1

Included and excluded articles

Article	Reason for exclusion or inclusion
Caritis SN, Venkataramanan R, Thom E, Harper M, Klebanoff MA, Sorokin Y, et al. Relationship between 17-alpha hydroxyprogesterone caproate concentration and spontaneous preterm birth. <i>Am J Obstet Gynecol.</i> 2014;210(2):128.e1-6.	Part of previous study (Harper 2010)
Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, et al. DHA supplementation and pregnancy outcomes. <i>Am J Clin Nutr.</i> 2013;97(4):808-15.	Not high-risk pregnancies
Harper M, Li L, Zhao Y, Klebanoff MA, Thorp JM, Jr., Sorokin Y, et al. Change in mononuclear leukocyte responsiveness in midpregnancy and subsequent preterm birth. <i>Obstet Gynecol.</i> 2013;121(4):805-11.	Part of previous study. (Harper 2010)
Harper M, Thom E, Klebanoff MA, Thorp J, Sorokin Y, Varner MW, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: A randomized controlled trial. <i>Obstet Gynecol.</i> 2010;115(2 PART 1):234-42.	Fulfills all criteria: included
Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P, et al. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: A randomized controlled trial. <i>J Am Med Assoc.</i> 2010;304(15):1675-83.	Not high-risk pregnancies
Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Gluud C. Randomised clinical trials of fish oil supplementation in high risk pregnancies. <i>Br J Obstet Gynaecol.</i> 2000;107(3):382-95.	Fulfills all criteria: included
Olsen SF, Østerdal ML, Salvig JD, Weber T, Tabor A, Secher NJ. Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: A randomised clinical trial with fish oil. <i>Eur J Clin Nutr.</i> 2007;61(8):976-85.	Part of previous study (Olsen 2000)
Ramakrishnan U, Stein AD, Parra-Cabrera S, Wang M, Imhoff-Kunsch B, Juárez-Márquez S, et al. Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: Randomized, double-blind, placebo-controlled trial in Mexico. <i>Food Nutr Bull.</i> 2010;31(2 SUPPL.):S108-S16.	Not high-risk pregnancies

Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. <i>Obstet Gynecol.</i> 2003;101(3):469-79.	Fortification, not supplementation
Imhoff-Kunsch B, Stein AD, Martorell R, Parra-Cabrera S, Romieu I, Ramakrishnan U. Prenatal docosahexaenoic acid supplementation and infant morbidity: Randomized controlled trial. <i>Pediatrics.</i> 2011;128(3):e505-e12.	Not high-risk pregnancies
Olsen SF, Sørensen JD, Secher NJ, Hedegaard M, Henriksen TB, Hansen HS, et al. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. <i>Lancet.</i> 1992;339(8800):1003-7.	Not high-risk pregnancies
Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. <i>Br J Obstet Gynaecol.</i> 1995;102(2):95-100.	Fulfills all criteria: included
Helland IB, Saugstad OD, Smith L, Saarem K, Solvoll K, Ganes T, et al. Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. <i>Pediatrics.</i> 2001;108(5):E82.	Not high-risk pregnancies
Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. <i>Pediatrics.</i> 2003;111(1):e39-44.	Part of previous study (Helland 2001)
Lucia Bergmann R, Bergmann KE, Haschke-Becher E, Richter R, Dudenhausen JW, Barclay D, et al. Does maternal docosahexaenoic acid supplementation during pregnancy and lactation lower BMI in late infancy? <i>J Perinat Med.</i> 2007;35(4):295-300.	Not high-risk pregnancies
Zhou SJ, Yelland L, McPhee AJ, Quinlivan J, Gibson RA, Makrides M. Fish-oil supplementation in pregnancy does not reduce the risk of gestational diabetes or preeclampsia. <i>Am J Clin Nutr.</i> 2012;95(6):1378-84.	Not high-risk pregnancies
Freeman MP, Davis M, Sinha P, Wisner KL, Hibbeln JR, Gelenberg AJ. Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. <i>J Affect Disord.</i> 2008;110(1-2):142-8.	Pregnancy duration not a listed study outcome

<p>Dunstan JA, Mori TA, Barden A, Beilin LJ, Holt PG, Calder PC, et al. Effects of n-3 polyunsaturated fatty acid supplementation in pregnancy on maternal and fetal erythrocyte fatty composition. <i>Eur J Clin Nutr.</i> 2004;58(3):429-37.</p>	<p>Not high-risk pregnancies</p>
<p>Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: A randomized, controlled trial. <i>J Allergy Clin Immunol.</i> 2003;112(6):1178-84.</p>	<p>Study excluded preterm births</p>
<p>Gould JF, Makrides M, Colombo J, Smithers LG. Randomized controlled trial of maternal omega-3 long-chain PUFA supplementation during pregnancy and early childhood development of attention, working memory, and inhibitory control. <i>Am J Clin Nutr.</i> 2014;99(4):851-9.</p>	<p>Study excluded preterm births</p>
<p>Helland IB, Saugstad OD, Saarem K, Van Houwelingen AC, Nylander G, Drevon CA. Supplementation of n-3 fatty acids during pregnancy and lactation reduces maternal plasma lipid levels and provides DHA to the infants. <i>J Matern-Fetal Neonatal Med.</i> 2006;19(7):397-406.</p>	<p>Part of previous study (Helland 2001)</p>
<p>Imhoff-Kunsch B, Briggs V, Goldenberg T, Ramakrishnan U. Effect of n-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: A systematic review. <i>Paediatr Perinat Epidemiol.</i> 2012;26(SUPPL. 1):91-107.</p>	<p>Systematic review</p>
<p>Knudsen VK, Hansen HS, Østerdal ML, Mikkelsen TB, Mu H, Olsen SF. Fish oil in various doses or flax oil in pregnancy and timing of spontaneous delivery: A randomised controlled trial. <i>BJOG Int J Obstet Gynaecol.</i> 2006;113(5):536-43.</p>	<p>Not high-risk pregnancies</p>
<p>Malcolm CA, McCulloch DL, Montgomery C, Shepherd A, Weaver LT. Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: A double blind, prospective, randomised trial. <i>Arch Dis Child Fetal Neonatal Ed.</i> 2003;88(5):F383-F90.</p>	<p>Not high-risk pregnancies</p>

Mulder KA, King DJ, Innis SM. Omega-3 fatty acid deficiency in infants before birth identified using a randomized trial of maternal DHA supplementation in pregnancy. PLoS ONE. 2014;9(1).	Not high-risk pregnancies
Olsen SF, Hansen HS, Secher NJ, Jensen B, Sandstrom B. Gestation length and birth weight in relation to intake of marine n-3 fatty acids. BR J NUTR. 1995;73(3):397-404.	Not a RCT
Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddle R, Gibson RA, et al. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: Randomised controlled trial. BMJ (Online). 2012;344(7845):14.	Part of previous study (Makrides 2010)
Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddle R, Gibson RA, et al. Randomized controlled trial of fish oil supplementation in pregnancy on childhood allergies. Allergy Eur J Allergy Clin Immunol. 2013;68(11):1370-6.	Part of previous study (Makrides 2010)
Pietrantonio E, Del Chierico F, Rigon G, Vernocchi P, Salvatori G, Manco M, et al. Docosahexaenoic acid supplementation during pregnancy: A potential tool to prevent membrane rupture and preterm labor. Int J Mol Sci. 2014;15(5):8024-36.	Not high-risk pregnancies
Ray JG. Fish oil supplementation reduced the recurrence of preterm delivery but not IUGR or hypertension. Evid-based Obstet Gynecol. 2000;2(4):95.	Not a RCT
Van Houwelingen AC, Sorensen JD, Hornstra G, Simonis MMG, Boris J, Olsen SF, et al. Essential fatty acid status in neonates after fish-oil supplementation during late pregnancy. BR J NUTR. 1995;74(5):723-31.	Part of previous study (Olsen 1992)
Bulstra-Ramakers MT, Huisjes HJ, Visser GH. The effects of 3g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension. Br J Obstet Gynaecol. 1995;102(2):123-6.	PD not a stated outcome measure.

