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# Fish Oil Supplementation does not Reduce Risks of Gestational Diabetes Mellitus, Pregnancy-Induced Hypertension, or Pre-Eclampsia: A Meta-Analysis of Randomized Controlled Trials

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** The effects of gestational supplementation with fish oil on risks for gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), and pre-eclampsia (PE) have not been confirmed. In this study, a meta-analysis was performed to evaluate the effect of fish oil supplementation on these gestational complications.


**Material/Methods:** Randomized controlled human trials that investigated the effects of fish oil supplementation in pregnant women were identified by a systematic search of Medline, Embase, and Cochrane's Library, and references of related reviews and studies up to December 2014. Relative risks (RRs) for GDM, PIH, and PE were the outcomes of interest. Fixed-effects or random-effects models were applied according to the heterogeneity.

**Results:** Thirteen comparisons from 11 published articles, including more than 5000 participants, were included. The results showed that fish oil supplementation was not associated with reduced risks for GDM (RR=1.06, 95% confidence interval [CI]: 0.85–1.32, p=0.60), PIH (RR=1.03, 95% CI: 0.89–1.20, p=0.66), or PE (RR=0.93, 95% CI: 0.74–1.16, p=0.51). No statistically significant heterogeneity was detected for the comparison of each outcome. The effects of fish oil on these gestational complications were consistent between women with low-risk and high-risk pregnancies.

**Conclusions:** Gestational supplementation with fish oil during the second or third trimester of pregnancy is not associated with reduced risks for GDM, PIH, or PE. Other possible benefits of fish oil supplementation during pregnancy warrant further evaluation.

**MeSH Keywords:** **Diabetes, Gestational • Fish Oils • Pre-Eclampsia**

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## Background

Gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), and pre-eclampsia (PE) have been recognized as the most common complications during pregnancy and seriously affect the health of both mothers and infants [1,2]. Although the prevalence of GDM and PE varies between different populations according to various diagnostic criteria, it has been noted that the incidences of these gestational complications are increasing worldwide [3,4]. Previous studies have revealed that maternal presence of GDM or PE increases the risk of perinatal adverse outcomes and that these complications can also lead to long-term health problems for mothers and children. Women with a history of GDM have been found to have higher risk for the development of type 2 diabetes mellitus and, more importantly, these women have been shown to be more vulnerable to future vascular lesions [5,6]. As for the children from pregnancies complicated by GDM, recent studies suggested that these children are at higher risk for the development of obesity and metabolic syndrome in their lifetime [7,8]. Similarly, the presence of PE, another serious complication in pregnancy characterized by new-onset hypertension and proteinuria, has also been related to an increased risk for cardiovascular diseases for the mothers [9]. Therefore, there is an urgent need to prevent the incidences of both the diabetic and hypertensive complications during pregnancy [10].

It has been suggested that gestational supplementation with fish oil, which mainly consists of 2 categories of marine omega 3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), may have pluripotential benefits for mothers and children [11,12], including elongation of gestational time and thus a lower risk of pre-term delivery [13] and improvements in growth measurements of infants [14], as well as cognitive function in children [15]. Early epidemiologic studies suggested that the dietary composition of n-3 PUFAs during pregnancy may reduce the risk for GDM [16,17]. However, further randomized controlled trials (RCTs) did not support that gestational supplementation with fish oil can reduce the risks for GDM, PIH, or PE. Some of the RCTs included few pregnant women and lacked statistical power, which may have confounded the negative results; therefore, in this study we performed a meta-analysis of relevant RCTs to evaluate the effects of fish oil supplementation on the risks of gestational diabetic and hypertensive complications.

## Material and Methods

We performed this meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [18] and the Cochrane Handbook guidelines [19].

## Database searching

PubMed, Embase, and the Cochrane Library (Cochrane Center Register of Controlled Trials) were searched systematically for related studies, using the terms “omega-3 fatty acids”, “fish oil”, “fish-oil”, “polyunsaturated fatty acids”, “marine oil”, “eicosapentaenoic acid”, “docosahexaenoic acid”, “DHA”, “EPA” paired with “pregnant”, “maternal”, “prenatal”, “pregnancy”, or “gestation”, with the limitation of studies in humans. The final search was performed on December 25, 2014. We also manually searched references of the original and review articles for possible related studies.

## Study selection

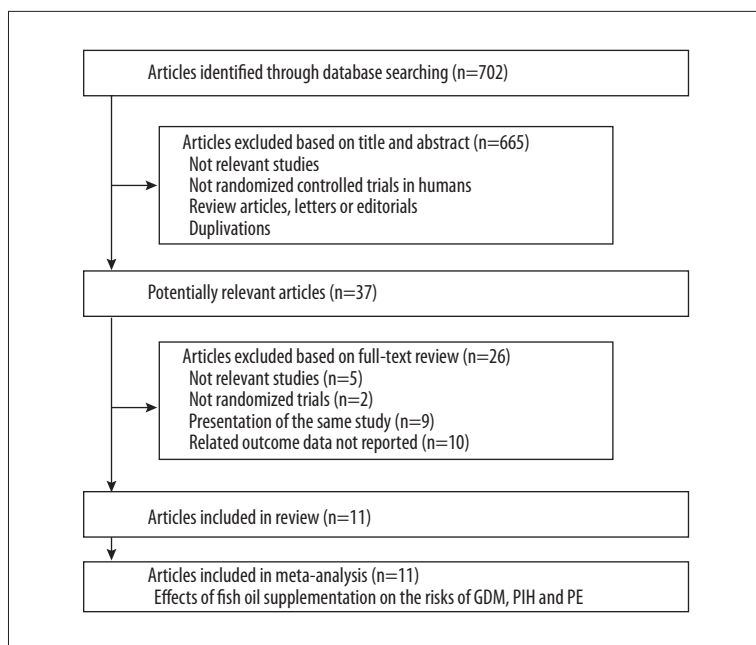
Studies were included if they met all of the following criteria: 1) published as a full-length article in English only; 2) reported as an RCT; 3) recruited pregnant women who were assigned to either an oral fish oil treatment group or a control group (no treatment or placebo), or they had a concomitant intervention for which the effects of fish oil could be separated; 4) fish oil was administered orally for at least 2 weeks; and 5) reported the incidence of at least 1 of the following events: GDM, PIH, or PE, or the incidence of the events could be calculated. The definitions and diagnostic criteria of GDM, PIH, and PE were in accordance with the original studies [20].

## Data extraction and quality assessment

Two of the authors (Bing Chen and Xinran Ji) independently performed the literature search, data extraction, and quality assessment according to the inclusion criteria. Discrepancies were resolved by consensus. Data regarding study design characteristics (parallel or crossover, blind, or open-label), locations of the studies, characteristics of the included pregnant women, numbers of the participants, components of the fish oil (doses of DHA and EPA) and controls, and of the gestational time (in weeks) of supplementation initiation were extracted. The corresponding authors of the original articles were contacted for unreported data. We used the 7 domains of the Cochrane Risk Of Bias tool to evaluate the quality of the included studies, which include criteria concerning aspects of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other potential threats to validity [19].

## Statistical analyses

Dichotomous data were analyzed using risk ratios (RRs) with 95% confidence intervals (CIs). Heterogeneity among the included studies was tested using Cochrane’s Q test, and significant heterogeneity was considered if the p value was <0.10. The I<sup>2</sup> statistic, indicating the percentage of total variation across studies



**Figure 1.** Flow diagram of the study selection procedure.

that is due to heterogeneity rather than chance [21], was also determined, and a value of  $I^2 > 50\%$  suggested significant heterogeneity [22]. Fixed-effects models were applied if no significant heterogeneity was detected by Cochrane's Q test, whereas random-effects models were used if there were significant heterogeneity across studies. We defined women from the general population to have low-risk pregnancies, while women with a history of preterm delivery, PIH, or intrauterine growth retardation and women with current double gestation were considered to have high-risk pregnancies as defined by the original studies. Subgroup analyses were performed to evaluate the impact of pregnancy risk on the outcomes. Additionally, publication bias was detected with Egger regression test [23] and visual inspection of the symmetry of the funnel plots. Statistical significance was considered at  $p < 0.05$ . We used RevMan software (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (Version 12.0; Stata Corporation, College Station, TX) for the process of meta-analysis and statistical analysis.

## Results

### Search results

The literature screening process is outlined in Figure 1. Briefly, a total of 702 published articles were obtained in the initial database search, and 665 were excluded, mainly because they were not relevant to the objective of the study. Of the 37 potentially relevant articles, 11 articles [24–34] met the inclusion criteria for the current meta-analysis. Twenty-six articles were excluded because 5 of them were not relevant studies, 2 were not RCTs, 9 were duplicated publications, and 10 did not report related outcome data.

### Study characteristics

The general characteristics of the included studies are listed in Table 1. One article [27] reported 4 prophylactic trials and 2 therapeutic trials, of which 2 trials reported data of PIH (Olsen 2000-Earl PIH and Olsen 2000-twins) and 2 trials reported data of PE (Olsen 2000-PE and Olsen 2000-twins). These trials were included separately. Another trial [33] included 2 study arms in which the pregnant women were supplied mainly with DHA (Mozurkewich 2013-DHA) or EPA (Mozurkewich 2013-EPA), and these 2 study arms were compared to the controls separately as 2 independent studies. The sample size of the control group was therefore equally distributed to the 2 study arms to overcome a unit of analysis error as recommended by the Cochrane's Handbook [19]. Therefore, 13 comparisons from 11 published articles were included in the current meta-analysis, all of which were performed in Western countries. Four articles included women who were considered to have high-risk pregnancies [25–27,31], while the other 7 articles included women with low-risk pregnancies who were generally healthy [24,28–30,32–34]. The dose of fish oil ranged from 200 to 4950 mg/d, with that for DHA from 0 to 2070 mg/d and that for EPA from 0 to 3000 mg/d. Supplementation with fish oil was initiated from the 14<sup>th</sup> to the 33<sup>rd</sup> weeks of gestation. No severe adverse events that were thought to be related to fish oil supplementation were reported by any included RCTs.

### Quality assessment

The results of risks of biases of the included studies as evaluated by the Cochrane assessment tool are shown in Table 2. Ten of the included RCTs were double-blinded placebo-controlled

**Table 1.** Characteristics of included studies.

Author year	Study design	Country	Participants	Number of participants	FO dose (mg/d)	DHA dose (mg/d)	EPA dose (mg/d)	Control	Initiation week (weeks)
Olsen 1992	R, SB	Denmark	Single pregnancy women	397	2200	920	1280	Olive oil or no treatment	30
Bulstra-Ramakers 1995	R, DB, PC	Netherlands	Pregnant women with history of IUGR	63	3000	0	3000	Coconut oil	14
Onwude 1995	R, DB, PC	UK	High-risk women for PIH and IUGR	232	2700	1080	1620	Air-filled capsule	27
Olsen 2000-prophylaxis	R, DB, PC	Multicenter in Europe	Pregnant women with history of IUGR, PD, PIH and double pregnancy	1477	2200	920	1280	Olive oil	20
Olsen 2000-prevention	R, DB, PC	Multicenter in Europe	High-risk women for PE and IUGR	142	4950	2070	2880	Olive oil	33
Smuts 2003a	R, DB, PC	USA	Healthy pregnant women	37	200	200	0	Ordinary eggs	26
Smuts 2003b	R, DB, PC	USA	Healthy pregnant women	291	200	200	0	Ordinary eggs	26
Goor 2010	R, DB, PC	Netherlands	Healthy pregnant women	78	250	220	30	Soybean oil	17
Harper 2010	R, DB, PC	USA	Pregnant women with history of PD	852	2000	800	1200	Inert mineral oil	22
Zhou 2012	R, DB, PC	Australia	Healthy pregnant women	2399	900	800	100	Vegetable oil	21
Carlson 2013	R, DB, PC	USA	Healthy pregnant women	301	600	600	0	Soybean and corn oil	20
Mozurkewich 2013-DHA	R, DB, PC	USA	Pregnant women at risk for depression	79	1080	900	180	Soy oil	18
Mozurkewich 2013-EPA	R, DB, PC	USA	Pregnant women at risk for depression	80	1334	274	1060	Soy oil	18

R – randomized; SB – single blind; DB – double-blind; PC – placebo-controlled; IUGR – intrauterine growth retardation; PD – preterm delivery; PIH – pregnancy-induced hypertension; PE – pre-eclampsia; FO – fish oil; EPA – eicosapentaenoic acid; DHA – ducosahexaenoic acid.

studies [25–34], while the other study was single-blinded [24]. Six studies reported methods of random sequence generation [26,27,31–34], and 7 studies reported details of allocation

concealment [24–27,31–33]. Details of withdrawals and drop-outs were reported in all studies.

**Table 2.** Cochrane risk of bias assessment.

	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats
Olsen 1992	Unclear	Yes	No	Unclear	Yes	Unclear	Unclear
Bulstra-Ramakers 1995	Unclear	Yes	Yes	Unclear	Yes	Unclear	Unclear
Onwude 1995	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Olsen 2000-prophylaxis	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Olsen 2000-prevention	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Smuts 2003a	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear
Smuts 2003b	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear
Goor 2010	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear
Harper 2010	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Zhou 2012	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Carlson 2013	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Mozurkewich 2013-DHA	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear
Mozurkewich 2013-EPA	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear

Yes – low risk of bias; Unclear – uncertain risk of bias; No – high risk of bias.

**Effects of fish oil supplementation on incidence of GDM**

Eight comparisons [28–34] (including 2064 women in the fish oil group and 2053 women in the control group), all in women with low-risk pregnancies, observed the effects of fish oil supplementation on the risk for GDM. The results of pooled analysis with a fixed-effects model showed that fish oil supplementation was not related to a reduced risk of GDM (RR=1.06, 95% CI: 0.85–1.32, p=0.60; Figure 2). No evidence of significant heterogeneity was detected (Cochrane’s Q test: p=0.50; I<sup>2</sup>=0%).

**Effects of fish oil supplementation on incidence of PIH**

Meta-analysis of 6 comparisons [24–27,32], including 2049 women in the fish oil group and 2081 in the control group, showed that fish oil supplementation was not associated with a reduced incidence of PIH (RR=1.03, 95% CI: 0.89–1.20, p=0.66; Figure 3). No evidence of significant heterogeneity was detected (Cochrane’s Q test: p=0.62; I<sup>2</sup>=0%). Moreover, subgroup analyses indicated that the results were consistent between women with low-risk (RR=0.93, 95% CI: 0.72–1.20, p=0.60) and high-risk (RR=1.11, 95% CI: 0.93–1.34, p=0.26) pregnancies.

**Effects of fish oil supplementation on incidence of PE**

The results of pooling the 12 comparisons [24–29,31–34] (including 2831 women in the fish oil group and 2854 women

in the control group) did not support a protective role of fish oil supplementation on the risk of PE (RR=0.93, 95% CI: 0.74–1.16, p=0.51; Figure 4). No evidence of significant heterogeneity was detected (Cochrane’s Q test: p=0.40; I<sup>2</sup>=5%). Moreover, subgroup analyses indicated that the results were consistent between women with low-risk (RR=0.85, 95% CI: 0.62–1.16, p=0.31) and high-risk (RR=1.02, 95% CI: 0.73–1.43, p=0.90) pregnancies.

**Publication bias**

The funnel plots for the effects of fish oil supplementation on the risks for GDM, PIH, and PE were symmetrical on visual inspection, suggesting no significant publication biases (figures not shown). Egger’s significance tests also did not indicate the existence of publication biases (for GDM, p=0.28; for PIH, p=0.18; for PE, p=0.37).

**Discussion**

In this meta-analysis, by pooling the results of all available RCTs, we found that gestational supplementation with fish oil during the second or third trimester of pregnancy is not associated with a reduced risk for GDM, PIH, or PE. These results are consistent in both low-risk and high-risk pregnancies. The potential benefits of fish oil supplementation during

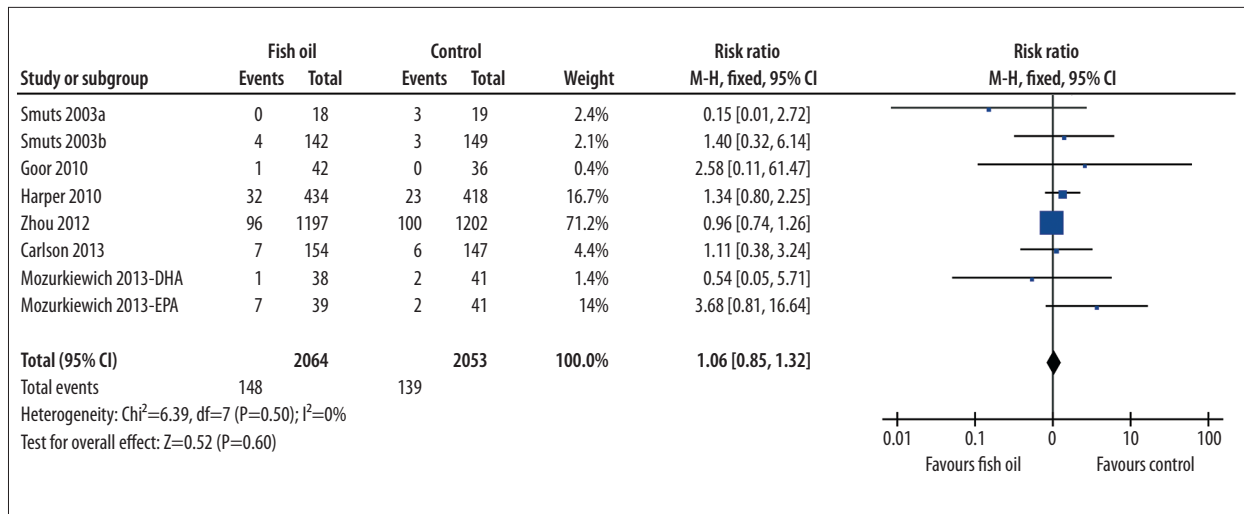


Figure 2. Forest plot from meta-analysis of risk ratio (RR) of gestational diabetes mellitus for pregnant women randomized to a fish oil or control group.

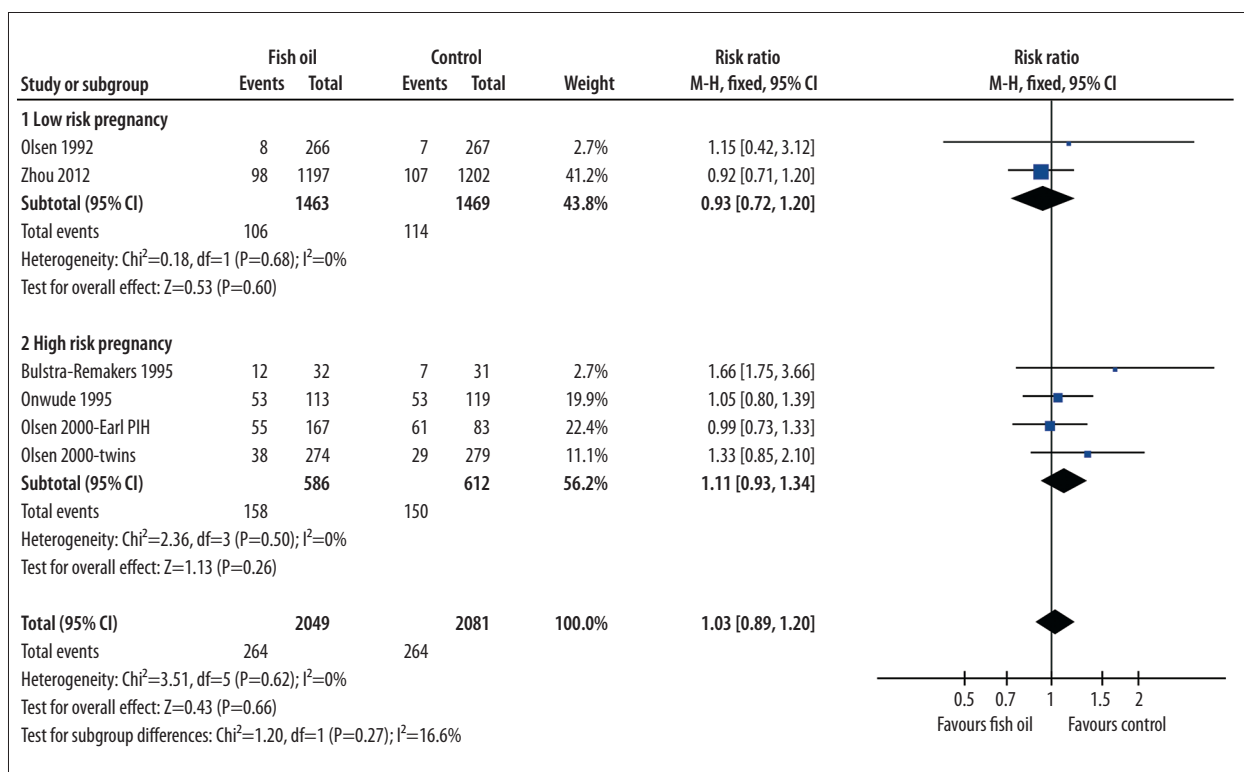


Figure 3. Forest plot from meta-analysis of risk ratio (RR) of pregnancy-induced hypertension for pregnant women (low-risk and high-risk) randomized to a fish oil or control group.

pregnancy on other maternal outcomes should be evaluated in future studies.

Although there have been a few meta-analyses aiming to evaluate the effects of gestational supplementation with fish oil on the incidence complications during pregnancy [14,35–37], ours, to the best of our knowledge, is the largest meta-analysis

including all available RCTs to date. The results of some recently published high-quality RCTs [33,34] have rarely been included in previous meta-analyses. Although the results of previous meta-analyses also did not support a preventative role for gestational fish oil supplementation against GDM, PIH, or PE, the chances that the negative results were retrieved due to the limited numbers of included studies and participants

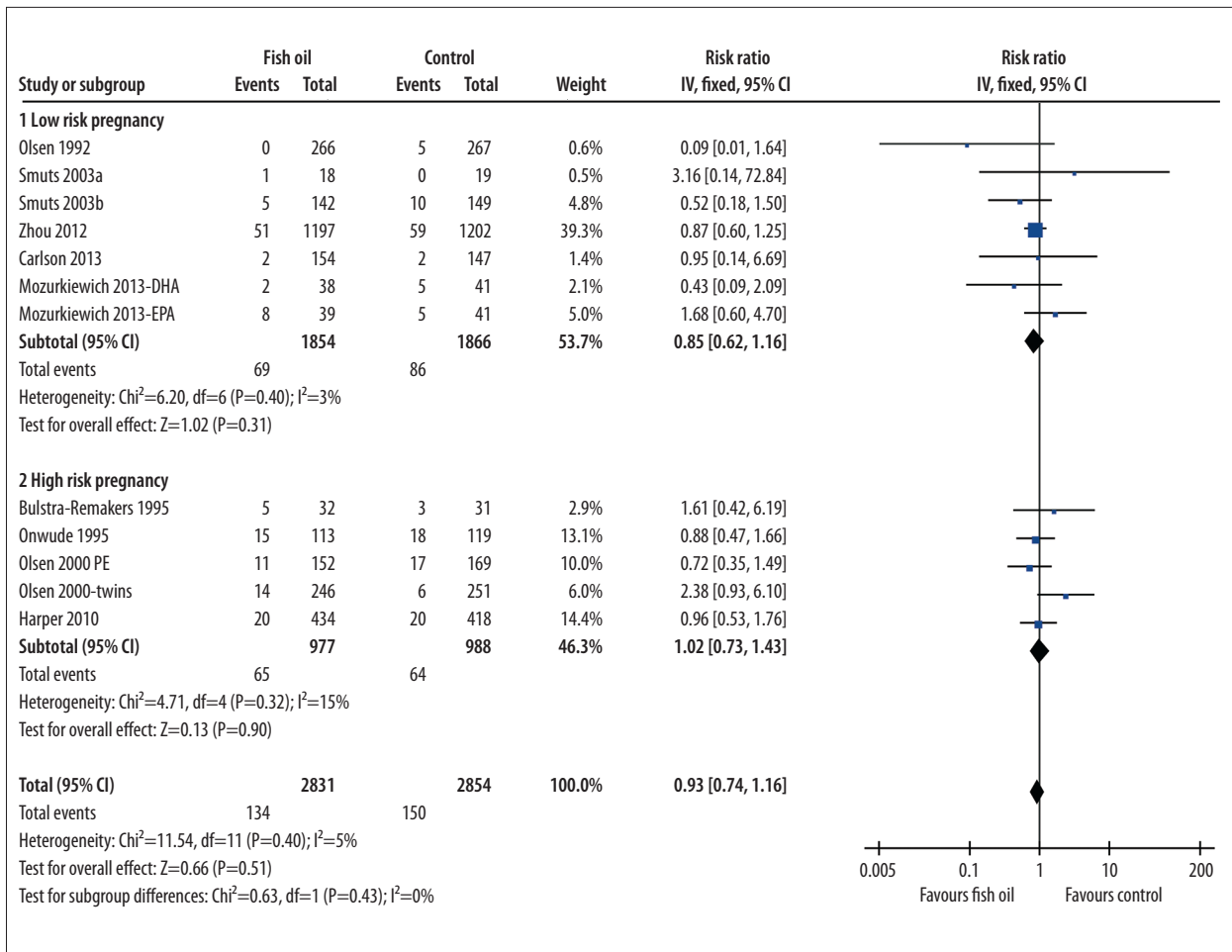


Figure 4. Forest plot from meta-analysis of risk ratio (RR) of pre-eclampsia for pregnant women (low-risk and high-risk) randomized to a fish oil or control group.

Table 3. Scale comparison of meta-analyses regarding the roles of n-3 PUFA on GDM, PIH, and PE.

	No. of comparisons (No. of participants)					
	GDM		PIH		PE	
Makrides 2006	–		5	(1831)	4	(1683)
Szajewska 2006	2	(328)	–		2	(328)
Horvath A 2007	–		3	(645)	2	(295)
Imhoff-Kunsch 2012	–		5	(1831)	4	(1683)
Current one	8	(4117)	6	(4130)	12	(5685)

n-3 PUFA – omega-3 polyunsaturated fatty acids; GDM – gestational diabetes mellitus; PIH – pregnancy-induced hypertension; PE – pre-eclampsia.

could not be totally excluded. Our meta-analysis, on the other hand, which includes 11 studies and about 5000 participants (Table 3) indicated that fish oil supplementation during pregnancy is not associated with reduced risks of gestational diabetic or hypertensive complications.

Routine supplementation of DHA or EPA during pregnancy should not be denied based on our results, because gestational fish oil supplementation may have other potential benefits. Accumulating evidence suggests that regular supplementation with fish oil during pregnancy may improve the body

measurements of the infants, which may reduce the risk of low birth weight [14]. In addition, a previous meta-analysis suggested that fish oil administered in pregnancy may reduce the rate of preterm birth [13]. Other than growth outcomes, recent studies also raised the possibility that n-3 PUFA supplementation during pregnancy may improve the cognitive or visual development of the children [15]. More importantly, in view of the fact that fish oil has been proved to confer various cardiovascular benefits, possibly through its anti-inflammatory effects [38] and improvement of endothelial function [39], whether gestational supplementation with fish oil can reduce the risk of cardiovascular diseases in mothers and children still needs to be clarified.

Our study has a few limitations that must be considered when interpreting the results. First, fish oil supplementation was initiated during the second or third trimester of pregnancy. Whether early supplementation of fish oil may affect the incidence of GDM, PIH, and PE needs to be determined in the future. Moreover, the baseline body composition and the habitual dietary contents of n-3 PUFAs were not evaluated or controlled in the included studies, which may affect the results of the meta-analysis. In addition, according to the study

by Zhou et al. [32], their sample size of more than 2000 women was sufficiently powered to discover a 3% reduction in absolute reduction in the risk of GDM. However, our study did not provide a sample size calculation to determine the statistical power of the current study. Finally, all of the studies were performed in Western countries. Whether gestational fish oil supplementation can benefit women in less developed countries should be studied in the future.

## Conclusions

The results of our meta-analysis indicate that gestational supplementation with fish oil during the second and third trimesters of pregnancy is not associated with reduced risks for GDM, PIH, or PE. Further studies are needed to evaluate other potential benefits of gestational fish oil supplementation to mothers and infants.

## Competing interests

The authors declare no competing interests.

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