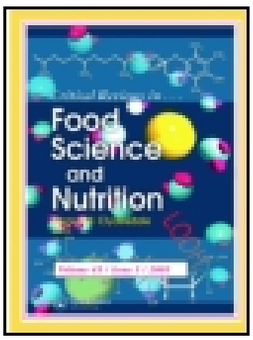

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REVIEW

The effect of maternal seafood consumption on perinatal outcomes: a systematic review and dose-response meta-analysis

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ABSTRACT

Observational studies have suggested inconsistent results between maternal seafood consumption and the risk of adverse birth outcomes. We aimed to explore the possible dose-response relationship between seafood consumption during pregnancy and perinatal outcomes. A systematic search was performed with the use of PubMed, Web of Science, Embase and Cochrane Library from inception to October 27, 2019. Random-effects model was used to estimate pooled odds ratios (ORs) and 95% confidence intervals (CIs). Dose-response meta-analysis was carried out by using generalized least-squares regression and restricted cubic splines. Twenty-one studies with a total of 571641 participants were included in the analyses. A 45 g/day increment in seafood consumption was associated with a reduced risk of low birth weight (LBW) (OR: 0.65, 95% CI: 0.47 to 0.90) and small for gestational age (SGA) (OR: 0.84, 95% CI: 0.71 to 0.98). Additionally, there was a non-linear dose-response relationship between maternal seafood consumption and the risk of preterm birth (PTB), with no further benefit observed when intake above 45 g/day. The results for subtypes of seafood showed a modest J-shaped association between fatty fish and PTB, and the lowest risk was observed with the consumption of 30 g/day. In conclusion, higher total seafood consumption during pregnancy was associated with a lower risk of adverse birth outcomes, but the consumption of fatty fish should not exceed 30 grams per day. These findings could provide substantial evidence for dietary recommendations regarding seafood intake for pregnant women. This review was registered in PROSPERO (CRD42020152912).

KEYWORDS

Low birth weight; meta-analysis; preterm birth; seafood; small for gestational age

Introduction

Adverse birth outcomes including low birth weight (LBW), preterm birth (PTB) and small for gestational age (SGA) are considered as the most common cause of neonatal mortality (Goldenberg et al. 2008; Lawn et al. 2014; Lawn, Cousens, and Zupan 2005) and could affect long term development and increase the risk of chronic disease in adulthood (Abitbol and Rodriguez 2012; Barker et al. 1989; Barros and Victora 1999; Brufani et al. 2009). Maternal nutritional status as a modifiable factor has been proposed to play an essential role in preventing these adverse birth outcomes (Belkacemi et al. 2010; Nnam 2015).

Seafood is rich in high-quality protein, vitamins and other essential nutrients, including long-chain n-3 polyunsaturated fatty acids (n-3 LCPUFA), which have been suggested providing beneficial effects on pregnancy outcomes (Carlson et al. 2013; De Giuseppe, Roggi, and Cena 2014; Szajewska, Horvath, and Koletzko 2006). Although most dietary guidelines have recommended pregnant women to eat seafood during pregnancy (US Food and Drug Administration & US Environmental Protection Agency (US FDA & US EPA) 2019; Government of Canada 2017), the relationship between seafood and perinatal outcomes remains controversial. In the past few decades, several epidemiological studies have been published on maternal seafood consumption and risk of adverse birth outcomes, with results of beneficial (Brantsaeter et al. 2012, 2017; Canda, Sezer, and Demir 2011), null (Burch et al. 2014; Mohanty et al. 2015; Nykjaer et al. 2019) or even harmful effects (Halldorsson et al. 2007).

A previous meta-analysis (Leventakou et al. 2014), published in 2014, indicated that moderate intake of seafood was associated with a lower risk of PTB and had no significant relationship with the risk of LBW and SGA. However, this meta-analysis only pooled the European birth cohort studies, and it only compared high intake group with low intake and did not further investigate the dose-response relationship between maternal seafood consumption and the risk of adverse birth outcomes. Moreover, several observational studies (Amezcua-Prieto et al. 2018; Brantsaeter et al.

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2017; Le Donne et al. 2016; Mohanty et al. 2016; Mohanty et al. 2015; Nykjaer et al. 2019; Smid et al. 2019) have been issued since the previous meta-analysis published. Therefore, it is essential to quantitatively assess the association between maternal seafood consumption and perinatal outcomes from the available evidence.

The objective of this study was to provide updated evidence to evaluate the association of maternal seafood consumption on the risk of LBW, PTB and SGA by conducting the dose-response meta-analysis. We also examined the dose-response relationships of different subtypes of seafood (lean fish, fatty fish, and shellfish) with perinatal outcomes. Our findings may provide dietary guidance for pregnant women regarding the choice of seafood intake during pregnancy, and further understanding of this topic may have significant public health implications.

Methods

Search strategy

This meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al. 2009) (see Supplemetry material Table S1 in Appendix 1). The review was registered in the PROSPERO, the International Prospective Register of Systematic Reviews (Registration number: CRD42020152912).

We systematically searched PubMed, Web of Science, Embase and the Cochrane Library from their inception to 27 October 2019 (date of the last search). Studies using the following terms for literature search: ("Seafood" OR "fish" OR "shellfish") AND ("Gestational Age" OR "Birth Weight" OR "Low Birth Weight" OR "Premature Birth" OR "Small for Gestational Age" OR "Pregnancy Complications" OR "Fetal growth" OR "Birth outcome") AND ("pregnant" OR "maternal" OR "prenatal" OR "pregnancy" OR "gestational"). Details of the search strategy are provided in supplementary materials (see Appendix 2). Furthermore, we manually screened the reference lists of the relevant studies.

Study selection

Two investigators (ZR and GQ) screened all the studies independently to assess the eligibility. The inclusion criteria were as follows: (i) studies were cohort or case-control design; (ii) used maternal seafood consumption as the exposure of the study; (iii) treated low birth weight (LBW, birthweight $<$ 2,500 grams [g]), preterm birth (PTB, $<$37 weeks' of gestation), and small for gestational age (SGA, birth weight $<$ 10th percentile for the gestational age) as the outcomes; (iv) reported risk estimates and 95% confidence intervals (CIs) on the outcomes; and (v) for dose-response analysis, studies should report at least three quantitative categories of seafood consumption and provided the numbers of cases and participants in each category. We excluded letters, commentaries, editorials, reviews without original data, and duplicated studies. We also excluded articles not published in English.

Data extraction and quality assessment

Two independent investigators (ZR and GQ) extracted the following information from eligible studies: first author's last name, year of publication, country, the study name, study period, sample size, dietary assessment methods, type of outcomes (LBW, PTB and SGA), mean age or age range, number of participants/cases, seafood intake in each category, risk estimates (OR and 95% CI) for each exposure category and covariates adjusted in the multivariate analysis. Newcastle Ottawa Quality Assessment Scale (NOS) was used in our research to assess the quality of selected studies (Stang 2010). The scale included three aspects: selection, comparability, and outcomes (cohort study)/exposures (case-control study). We classified studies with a score of 7–9 as high-quality studies. Any disagreement was settled by group discussion.

Statistical methods

We used ORs and 95% CIs as the risk estimates for studies, and HRs and RRs were approximately assumed as ORs. Firstly, we used the random-effects model (DerSimonian and Laird 2015) to calculate the summary ORs of total and different subtypes of seafood consumption and LBW, PTB, and SGA for the highest versus lowest category. When studies (Guldner et al. 2007; Le Donne et al. 2016) did not report the results for total seafood, but reported risk estimates for different subtypes of seafood separately, we pooled these estimates using the fixed-effects model to obtain the summary ORs of total seafood intake.

We conducted linear dose-response analyses by random-effects model (Greenland and Longnecker 1992). The mean or median of seafood consumption and the corresponding risk estimates for at least three quantitative categories were needed. When studies reported the intake range, we estimated the midpoint between the lower and upper boundary of the exposure category. If the highest level of intake was open-ended, we used the width of the adjacent interval to calculate an upper bound. When the lower boundary of the lowest category was not reported, we considered it as zero. If seafood consumption was reported by servings, or times, we converted them into the standard serving, which was defined as 105 g according to He et al. (2004) to recalculate results. The linear dose-response results in the forest plots were presented for increments of 45 g/day (equal to 315 g/week) for seafood and specific subtypes of seafood.

To examine a potential non-linear dose-response relationship, we used restricted cubic splines with 3 knots at fixed percentiles (10th, 50th, and 90th) of the exposure data (Desquilbet and Mariotti 2010; Orsini et al. 2012). A likelihood ratio test was used to assess the non-linearity (Bagnardi et al. 2004; Desquilbet and Mariotti 2010). When the reference category was not the lowest, we used the method described by Hamling et al. (2008) to calculate new

risk estimates by setting the lowest category of seafood intake as the reference.

Heterogeneity among studies was assessed by Cochran's Q test ($P < 0.10$) and the I^2 statistic test (Higgins and Thompson 2002). I^2 values of 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity, respectively (Higgins et al. 2003). To explore the potential sources of heterogeneity among studies, we conducted the subgroup analyses and meta-regression (Thompson and Higgins 2002) for the highest versus lowest category based on study design (case-control and cohort studies), geographical location (Europe, America, Asia, and Oceania), sample size (<3000 and ≥3000), methods of dietary assessment (self-administered FFQ and in-person interview), whether there were adjustments for various confounders (maternal age, pre-pregnancy body mass index (BMI)/pre pregnant weight, maternal smoking status, maternal alcohol consumption, and energy intake), and study quality (<7 and ≥7).

We used the funnel plots, Egger's test (Egger et al. 1997) and Begg's test (Begg and Mazumdar 1994) to assess the publication bias. We performed sensitivity analyses to evaluate the stability of results by omitting one study in each turn. Besides, we also conducted the sensitivity analyses by excluding studies that did not adjust for any confounding factors in the overall risk estimates or studies with low-quality scores. Due to the limited number of included studies for specific subtypes of seafood, subgroup analyses, sensitivity analyses, and publication bias assessment only performed in total seafood consumption. All analyses were used with STATA, version 15.1 (StataCorp, College Station, TX). Statistical tests were two-tailed at the significance level of $P < 0.05$.

Results

Literature search and study characteristics

Our literature search identified a total of 5864 articles. After the removal of duplicate records and the initial screening based on titles and abstracts, 84 articles included for further assessment. By full-text assessing, another 63 studies were excluded with the respective reasons for exclusion (see Supplemetry material Table S2 in Appendix 1). Finally, our meta-analysis included 21 eligible articles (Amezcua-Prieto et al. 2018; Brantsaeter et al. 2012, 2017; Burch et al. 2014; Canda, Sezer, and Demir 2011; Guldner et al. 2007; Halldorsson et al. 2007; Heppe et al. 2011; Klebanoff et al. 2011; Le Donne et al. 2016; Mendez et al. 2010; Mitchell et al. 2004; Mohanty et al. 2016; Mohanty et al. 2015; Muthayya et al. 2009; Nykjaer et al. 2019; Olsen and Secher 2002; Ricci et al. 2010; Rogers et al. 2004; Rylander, Stromberg, and Hagmar 1996; Smid et al. 2019) from 19 independent cohort studies, with a total of 571641 participants and 65360 cases with adverse birth outcomes (11 studies reported LBW as the outcome of interest, 10 studies reported risk estimate for PTB and 9 studies for SGA) (see Figure 1). Of these studies, 14 studies were from Europe, 5 studies were from the United States, 1 study from Asia and 1 from Oceania. Seventeen studies were cohorts and four studies were case-control studies. The mean quality score of studies was 7, and 13 studies were of high quality (score ≥ 7) (see Supplemetry material Table S3 in Appendix 1). Most of the studies adjusted for maternal age, education levels, smoking status and pre-pregnancy BMI in their multivariate analyses, and some of the studies also controlled for fish oil (n = 9), energy intake (n = 8), and alcohol consumption (n = 8). Table 1 showed the characteristics of included studies.

Total seafood consumption during pregnancy and the risk of LBW

Eleven studies (Brantsaeter et al. 2012; Burch et al. 2014; Canda, Sezer, and Demir 2011; Guldner et al. 2007; Heppe et al. 2011; Mohanty et al. 2015; Muthayya et al. 2009; Nykjaer et al. 2019; Olsen and Secher 2002; Rogers et al. 2004; Rylander, Stromberg, and Hagmar 1996) with 445973 participants and 26823 cases were included in the analysis. The pooled OR of LBW for the highest versus lowest category of seafood consumption during pregnancy was 0.78 (95% CI: 0.61 to 1.00), with moderate heterogeneity (I^2=50.8%, $P_{heterogeneity}$=0.03) (see Figure 2, Table 2).

For the dose-response meta-analysis, we excluded two studies (Brantsaeter et al. 2012; Canda, Sezer, and Demir 2011) because of dividing seafood consumption only into two categories, and two studies (Burch et al. 2014; Muthayya et al. 2009) not reporting the number of cases. Only seven studies (Guldner et al. 2007; Heppe et al. 2011; Mohanty et al. 2015; Nykjaer et al. 2019; Olsen and Secher 2002; Rogers et al. 2004; Rylander, Stromberg, and Hagmar 1996) were incorporated into the dose-response meta-analysis with a total of 20254 participants and 869 cases. The linear dose-response analysis indicated that each 45 g/day increment in seafood consumption was associated with a 35% lower risk of LBW (OR: 0.65, 95% CI: 0.47 to 0.90). There was no evidence of heterogeneity ($I^2 = 0\%$, $P_{heterogeneity} = 0.51$) (see Figure 3, Table 2). In addition, we found no evidence of non-linear relationship between maternal seafood consumption and the risk of LBW ($P_{non\text{-}linearity}$ =0.51) (see Supplemetry material Figure S1 in Appendix 3).

Total seafood consumption during pregnancy and the risk of PTB

In terms of the risk of PTB, eleven studies (Brantsaeter et al. 2017; Burch et al. 2014; Guldner et al. 2007; Heppe et al. 2011; Klebanoff et al. 2011; Le Donne et al. 2016; Mohanty et al. 2016; Nykjaer et al. 2019; Olsen and Secher 2002; Rogers et al. 2004; Smid et al. 2019) were included in the meta-analysis, with 451965 participants and 36391 cases. The pooled OR for the highest versus lowest category of seafood consumption was 0.90 (95% CI: 0.72 to 1.14), with significant evidence of heterogeneity ($I^2 = 76.7\%$, $P_{heterogeneity}$<0.001) (see Table 2, Supplemetry material Figure S2 in Appendix 3).

For the dose-response meta-analysis, two studies (Le Donne et al. 2016; Smid et al. 2019) were excluded due to providing only two categories, and two studies (Burch et al. 2014; Klebanoff et al. 2011) not reporting the number of cases. Seven studies (Brantsaeter et al. 2017; Guldner et al.

Table 1. Characteristics of included studies on maternal seafood consumption and perinatal outcomes.

Author, publication year, country	Study name, study type	Study period	No of participants	Age range or Mean age(years)	Dietary assessment method	Time of dietary assessment[a]	Categories of seafood consumption	Outcomes	NOS score	Adjusted variables
Brantsaeter et al. 2017, Norway	Norwegian Mother and Child Cohort Study (MoBa), Prospective Cohort	2003–2008	67007	NR	self- administered sFFQ	22 weeks	≤5 g/d >5–20 g/d >20–40 g/d >40–60 g/d >60 g/d	PTB	8	Maternal age, height, parity, pre-pregnancy BMI, energy intake, maternal education, smoking, marital status, household income, previous preterm delivery, other seafood categories and LCn-3PUFA from supplements
Brantsaeter et al. 2012, Norway	Norwegian Mother and Child Cohort Study (MoBa), Prospective Cohort	2002–2008	62099	NR	self- administered sFFQ	22 weeks	≤5 g/d >5–20 g/d >20–40 g/d >40–60 g/d >60 g/d	LBW	8	Maternal age, height, pre-pregnancy BMI, parity, pregnancy duration, maternal education, smoking status, mother tongue other than Norwegian, total energy intake, and with intakes of seafood/ seafood items and supplementary n-3 mutually adjusted
Canda, Sezer, and Demir 2011, Turkey	-, Prospective Cohort	2007.3–2008.9	442	30.1 ± 4.2 (18–43)	self- administered FFQ	>16 weeks	Low consumers High consumers	LBW SGA	6	/
Nykjaer et al. 2019, UK	The CARE Study, Prospective Cohort	2003–2006	1208	18–45	self- administered FFQ	first, second and third trimester	No take ≤2 portions/wk >2 portions/wk	LBW PTB SGA	8	Maternal age, height, parity, pre-pregnancy weight, ethnicity, salivary cotinine levels, caffeine intake, alcohol intake, education, gestation, baby's sex
Mohanty et al. 2015, USA	The Omega study, Prospective Cohort	1996–2008	3141	32.7 ± 4.3	self- administered sFFQ	first trimester	<0.2 serving/mo 0.2 serving/mo 0.5 serving/wk 0.5–1serving/wk >1 serving/wk	LBW	8	Maternal age, non-Hispanic white race, post high-school education, pre-pregnancy BMI, unmarried marital status, current recreational physical activity, total energy, current smoking, current alcohol intake, nulliparity, intake of red/ processed meats, male infant sex
Burch et al. 2014, USA	-, Retrospective Cohort	1995–2005	362625	25(11–51)	self- administered FFQ	after delivery	Do not eat 1 meal/mo 1 meal/wk No restrictions	LBW PTB	3	Mother's age, education, race, smoking status, number of previous live births and stillborns
Halldorsson et al. 2007, Denmark	Danish National Birth Cohort, Prospective Cohort	1996–2002	44824	NR	self- administered FFQ	25 weeks	≤5 g/d 5–20 g/d 20–40 g/d 40–60 g/d >60 g/d	SGA	7	Maternal age, height, pre-pregnancy BMI, gestational age, infant gender, parity, energy intake, smoking, familial socioeconomic status, paternal height
Smid et al. 2019, USA	Maternal Fetal Medicine Unit's Omega-3 trial, Prospective Cohort	2005.1–2006.10	852	23–32	self- administered FFQ	16–22.9 weeks	<1 servings/wk ≥1 portions/wk	PTB	6	Maternal age, race, pre-pregnancy BMI, education, smoking, number of prior previous PTB and gestational age at earliest PTB
Amezcua-Prieto et al. 2018, Spain	-, Case-control study	2012.5–2015.7	1036	NR	Interviewer- administered FFQ	after delivery	Q1 (≤56 g/d) Q2 (56.1–74.0 g/d) Q3 (74.1–92.6 g/d) Q4 (92.7–121 g/d) Q5 (>121g/d)	SGA	6	Maternal age, energy intake, educational level, smoking, pre-gestational BMI, previous preterm or low birthweight newborn
Mohanty et al. 2016, USA	The Omega study, Prospective Cohort	1997–2008	3279	32.7 ± 4.4	self- administered sFFQ	first trimester	<0.2 serving/mo 0.2 serving/mo 0.5 serving/wk 0.5–1serving/wk >1 serving/wk	PTB	8	Maternal age, non-Hispanic white race, post high-school education, pre-pregnancy BMI, unmarried marital status, current recreational physical activity, total energy, current smoking, current alcohol intake, nulliparity, intake of red/ processed meats, and male infant sex
Le Donne et al. 2016, Italy	-, Prospective Cohort	2013.4–2013.7	114	31 ± 1.4 (18–43)	Interviewer- administered FFQ	34 weeks	Not eat Eat	PTB	3	/

Guldner et al. 2007, France	PELAGIE cohort, Prospective Cohort	2002.4–2005.2	2301	30.2 ± 4.1	self- administered FFQ	first trimester	<1 time/mo 1–4 times/mo ≥2 times/wk	LBW PTB SGA	8	Maternal age, marital status, parity, BMI, height, smoking status, diabetes, sex of the child, education level, alcohol consumption, duration of gestation
Klebanoff et al. 2011, USA	-, Prospective Cohort	2005.1–2006.10	852	NR	Interviewer- administered FFQ	16–21 weeks	<1 servings/mo 1 servings/wk 2 servings/wk 3 servings/wk 4 servings/wk 5 servings/wk 6 servings/wk 7 servings/wk 8 servings/wk	PTB	8	Maternal age, BMI, study center, number of previous preterm births, gestation of earliest previous spontaneous preterm birth, receipt of omega-3 compared with placebo supplement, smoking, education, ethnicity
Heppe et al. 2011, The Netherlands	The Generation R Study, Prospective Cohort	2002–2006	3380	31.4 ± 4.4	Interviewer- administered sFFQ	first trimester	0 g/wk 1–69 g/wk 70–139 g/wk 140–209 g/wk >210 g/wk	LBW PTB SGA	9	Maternal age, BMI, marital status, education, smoking, energy intake, alcohol use, nausea, vomiting, use of folic acid supplements, gestational age at measurement, paternal height, fetal sex
Ricci et al. 2010, Italy	-, Case-control study	1989–1999	2521(case:555, control: 1966)	31	Interviewer- administered FFQ	after delivery	0 servings/wk 1 servings/wk ≥2 servings/wk	SGA	6	Maternal age, education, parity, body mass index, smoking habits, heavy alcohol consumption, gestational hypertension, history of SGA births, weight gain in pregnancy, gestational age
Mendez et al. 2010, Spain	the Childhood and Environment study (INMA), Prospective Cohort	2004.7–2006. 7	592	31.5 ± 4.4	Interviewer- administered sFFQ	first trimester	≤3 servings/wk 3–6 servings/wk >6 servings/wk	SGA	9	Maternal age, nulliparity, paternal BMI, maternal BMI, child sex, education, energy intakes, smoking during pregnancy, under- reporting, contaminants, Birth weight models were also adjusted for gestational age; models for seafood subtypes also adjust for other types of seafood
Muthayya et al. 2009, India	-, Prospective Cohort	2002.1–2006.3	676	17–40	Interviewer- administered FFQ	first and third trimester	Group1 Group2 Group3	LBW	9	Maternal age, maternal education, parity, maternal weight/ maternal weight gain per wk, gestational age
Rogers et al. 2004, England	the Avon longitudinal study of parents and children (ALSPAC), Prospective Cohort	1991.4–1992.12	11585	NR	self- administered FFQ	32 weeks	0 portions/wk 0.74 portions/wk 2.29 portions/wk 4.44 portions/wk	LBW PTB	7	Maternal age, smoking, parity, height, pre-pregnant weight, education, sex of infant, cohabitant status, alcohol consumption
Mitchell et al. 2004, New Zealand	The Auckland Birthweight Collaborative study, Case-control study	1995.10–1997. 11	1714	Case : 29.1 ± 5.7 Control : 30.3 ± 5.5	self- administered FFQ	after delivery	0 < 1 servings/wk ≥1 servings/wk	SGA	6	Maternal height, maternal weight before pregnancy, maternal hypertension, maternal smoking, ethnicity, socioeconomic status
Olsen and Secher 2002, Denmark	-, Retrospective Cohort	1992.6	1159	NR	self- administered FFQ	after delivery	FREQ 0 (0 g/d) FREQ 1 (3.1 g/d) FREQ 2 (12.4 g/d) FREQ 3 (44.3 g/d)	LBW PTB	8	Maternal age, maternal smoking, alcohol consumption, parity, height, prepregnant weight, length of education, cohabitant status
Rylander, Stromberg, and Hagmar 1996, Sweden	The Swedish East Coast, Nested Case-control study	1973–1991	234	NR	Interviewer- administered FFQ	after delivery	0–3 meals/mo 4–6 meals/mo ≥7 meals/mo	LBW	6	Maternal age and smoking habits during the calendar year of birth

Abbreviations: BMI, body mass index; CI, confidence interval; NR, not reported; SD, standard deviation; FFQ, food frequency questionnaire; sFFQ, semi-quantitative FFQ; mo, month; wk, week; d, day; LBW, low birth weight; PTB, preterm birth; SGA, small for gestational age for weight; NOS, Newcastle Ottawa scale.

aTime of dietary assessment represented the weeks of gestation when dietary assessment was performed using FFQ.

Table 2. Total and subtypes of seafood consumption on LBW, PTB, and SGA, the highest versus lowest analysis and dose-response analysis.

Subtype of seafood	Highest versus lowest analysis				Dose-response analysis				
	No of studies	OR (95% CI)	I^2 (%)	$P_{heterogenity}$	Increment(g/day)	No of studies	OR (95% CI)	I^2 (%)	$P_{heterogenity}$
LBW									
seafood	11	0.78(0.61–1.00)	50.80	0.03	45	7	0.65(0.47–0.90)	0.00	0.51
lean fish	2	1.71(0.95–3.08)	34.40	0.22	45	2	3.51(1.16–10.66)	0.00	0.43
fatty fish	4	0.84(0.57–1.23)	0.00	0.79	45	4	0.92(0.46–1.82)	0.00	0.69
shellfish	3	1.33(0.74–2.42)	52.80	0.12	45	3	1.23(0.26–5.83)	66.40	0.05
PTB									
seafood	11	0.90(0.72–1.14)	76.70	<0.001	45	7	0.84(0.70–1.01)	44.60	0.09
lean fish	4	1.05(0.67–1.66)	66.30	0.03	45	3	0.98(0.46–2.08)	63.60	0.06
fatty fish	5	0.85(0.65–1.11)	28.10	0.23	45	4	0.70(0.42–1.17)	55.80	0.08
shellfish	4	1.00(0.77–1.31)	0.00	0.73	45	3	0.79(0.51–1.23)	0.00	0.77
SGA									
seafood	9	0.79(0.59–1.06)	73.20	<0.001	45	7	0.84(0.71–0.98)	53.70	0.04
lean fish	4	0.91(0.73–1.15)	29.50	0.24	45	2	0.64(0.22–1.86)	37.80	0.21
fatty fish	5	0.96(0.68–1.36)	67.00	0.02	45	3	0.62(0.35–1.10)	36.30	0.21
shellfish	4	1.25(0.86–1.81)	65.50	0.03	45	3	1.37(0.89–2.10)	13.10	0.32

Abbreviations: OR, odds ratio; CI, confidence interval; LBW, low birth weight; PTB, preterm birth; SGA, small for gestational age for weight.

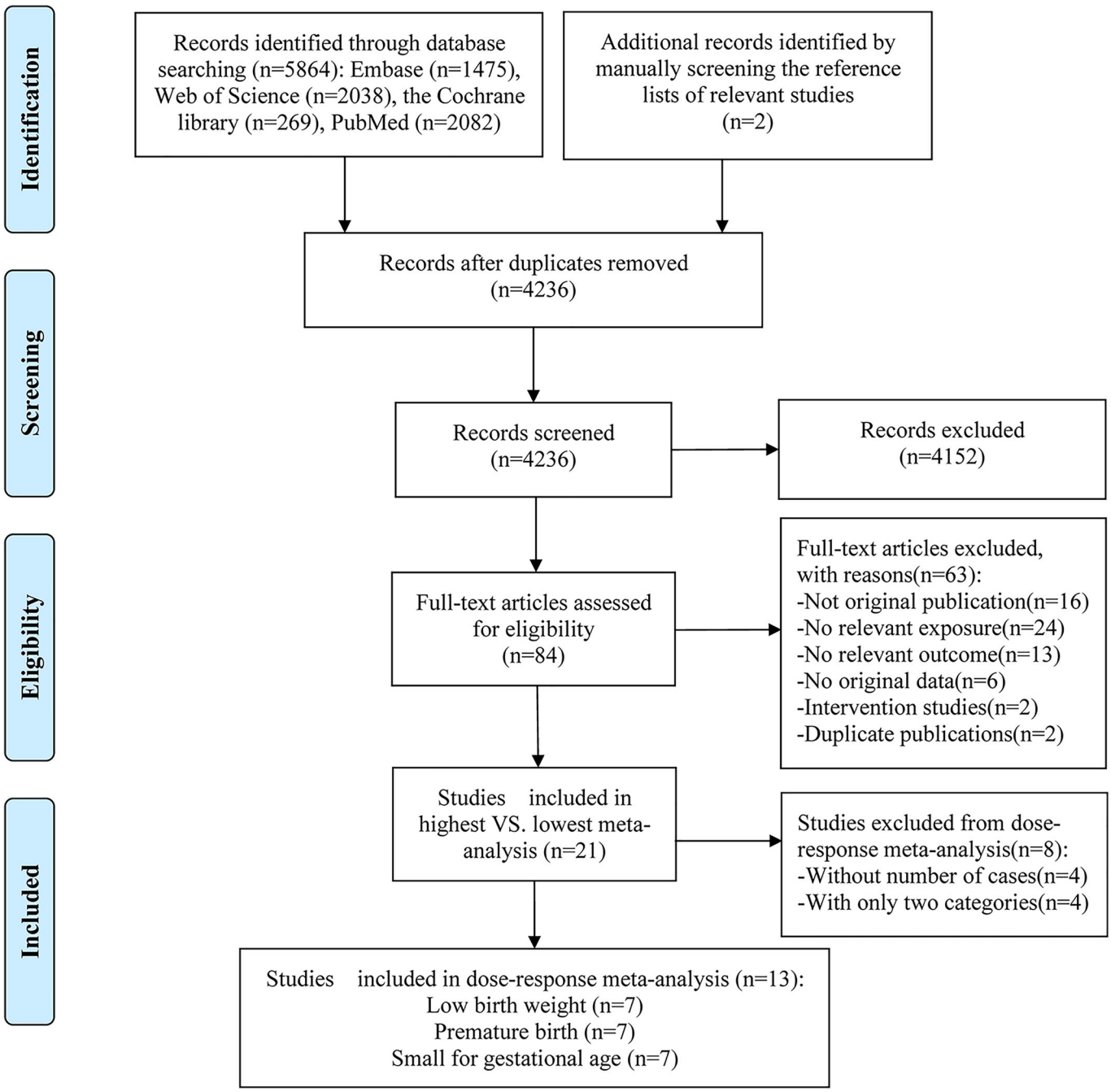

Figure 1. Study flow diagram.

Table 3. Subgroup analyses of maternal seafood consumption and LBW, PTB, and SGA.

		Low birth weight					Preterm birth					Small for gestational age				
Subgroup		No	OR (95% CI)	I^2 (%)	$P_h{}^1$	$P_h{}^2$	No	OR (95% CI)	I^2 (%)	$P_h{}^1$	$P_h{}^2$	No	OR (95% CI)	I^2 (%)	$P_h{}^1$	$P_h{}^2$
All studies		11	0.78(0.61–1.00)	50.80	0.03		11	0.90(0.72–1.14)	76.70	<0.001		9	0.79(0.59–1.06)	73.20	<0.001	
Study type																
Cohort		10	0.78(0.60–1.03)	54.50	0.02	0.85	11	0.90(0.72–1.14)	76.70	<0.001	NC	6	0.87(0.57–1.33)	71.20	0.004	0.42
Case–control		1	0.70(0.32–1.51)	—	—		0	—	—	—		3	0.72(0.59–0.88)	0.00	0.42	
Geographic location																
Europe		8	0.68(0.50–0.94)	31.30	0.18	0.54	7	0.79(0.55–1.14)	60.70	0.02	0.32	8	0.83(0.61–1.12)	72.80	0.001	0.52
America		2	1.20(0.61–2.37)	61.10	0.11		4	1.05(0.72–1.54)	79.90	0.002		0	—	—	—	
Asia		1	0.65(0.37–1.14)	—	—		0	—	—	—		0	—	—	—	
Oceania		0	—	—	—		0	—	—	—		1	0.59(0.37–0.94)	—	—	
Study quality																
<7		3	0.67(0.36–1.24)	69.10	0.04	0.54	3	0.85(0.56–1.30)	80.30	0.01	0.83	4	0.62(0.45–0.86)	51.00	0.11	0.07
≥7		8	0.80(0.57–1.11)	38.40	0.12		8	0.92(0.63–1.34)	71.90	0.001		5	1.05(0.77–1.42)	45.30	0.12	
Number of cases																
<3000		5	0.67(0.44–1.02)	19.90	0.29	0.49	5	0.71(0.48–1.05)	29.50	0.23	0.32	7	0.73(0.55–0.98)	55.80	0.04	0.34
≥3000		6	0.83(0.61–1.14)	58.40	0.04		6	1.00(0.77–1.31)	81.70	<0.001		2	1.00(0.56–1.77)	66.80	0.08	
Dietary assessment																
By interviewer		3	0.70(0.47–1.05)	0.00	0.88	0.74	3	1.40(0.79–2.46)	0.00	0.76	0.24	4	0.78(0.56–1.08)	39.80	0.17	0.90
Self–reported		8	0.79(0.57–1.10)	61.30	0.01		8	0.85(0.66–1.09)	82.70	<0.001		5	0.76(0.49–1.19)	79.60	0.00	
Adjusted for confounding factors																
Age	Yes	10	0.83(0.67–1.04)	38.20	0.10	0.10	9	0.96(0.75–1.22)	76.40	<0.001	0.48	7	0.91(0.69–1.19)	65.80	0.01	0.09
	No	1	0.30(0.12–0.76)	—	—		2	0.66(0.50–0.87)	0.00	0.49		2	0.45(0.22–0.90)	55.40	0.13	
BMI	Yes	8	0.80(0.57–1.11)	38.40	0.12	0.71	9	0.87(0.65–1.18)	70.60	0.001	0.66	8	0.86(0.66–1.12)	68.40	0.002	0.08
	No	3	0.67(0.36–1.24)	69.10	0.04		2	1.03(0.98–1.08)	0.00	0.69		1	0.28(0.12–0.66)	—	—	
Education	Yes	9	0.84(0.66–1.07)	42.80	0.08	0.20	10	0.90(0.71–1.14)	79.00	<0.001	0.69	6	0.81(0.64–1.03)	28.00	0.23	0.64
	No	2	0.48(0.21–1.09)	47.20	0.17		1	1.85(0.10–34.3)	—	—		3	0.64(0.29–1.41)	89.00	<0.001	
Energy intake	Yes	3	0.92(0.43–1.97)	67.00	0.05	0.69	3	1.10(0.60–2.02)	80.90	0.01	0.46	4	0.96(0.58–1.60)	75.20	0.01	0.35
	No	8	0.77(0.59–1.02)	45.40	0.08		8	0.84(0.62–1.15)	70.10	0.001		5	0.70(0.51–0.97)	55.00	0.06	
Smoking	Yes	8	0.85(0.66–1.09)	45.40	0.08	0.22	9	0.93(0.74–1.17)	79.70	<0.001	0.32	7	0.87(0.66–1.16)	71.80	0.002	0.18
	No	3	0.54(0.30–1.00)	25.50	0.26		2	0.46(0.10–2.04)	20.00	0.26		2	0.46(0.49–1.13)	63.50	0.10	
Alcohol	Yes	6	0.95(0.62–1.47)	31.80	0.20	0.26	6	0.89(0.55–1.45)	68.10	0.01	0.88	4	0.83(0.68–1.01)	0.00	0.57	0.88
	No	5	0.66(0.45–0.97)	69.20	0.01		5	0.85(0.63–1.14)	85.20	<0.001		5	0.77(0.44–1.33)	84.30	<0.001	
Fish oil	Yes	5	0.67(0.48–0.93)	26.20	0.25	0.28	6	0.81(0.56–1.18)	78.00	<0.001	0.43	2	1.02(0.60–1.74)	62.50	0.10	0.31
	No	6	0.88(0.62–1.27)	46.50	0.10		5	1.03(0.98–1.08)	0.00	0.47		7	0.73(0.54–0.98)	56.00	0.03	

Abbreviations: OR, odds ratio; CI, confidence interval; NC, not calculable.
$P_h{}^1$ for heterogeneity within each subgroup.
$P_h{}^2$ for heterogeneity between subgroups with meta-regression.

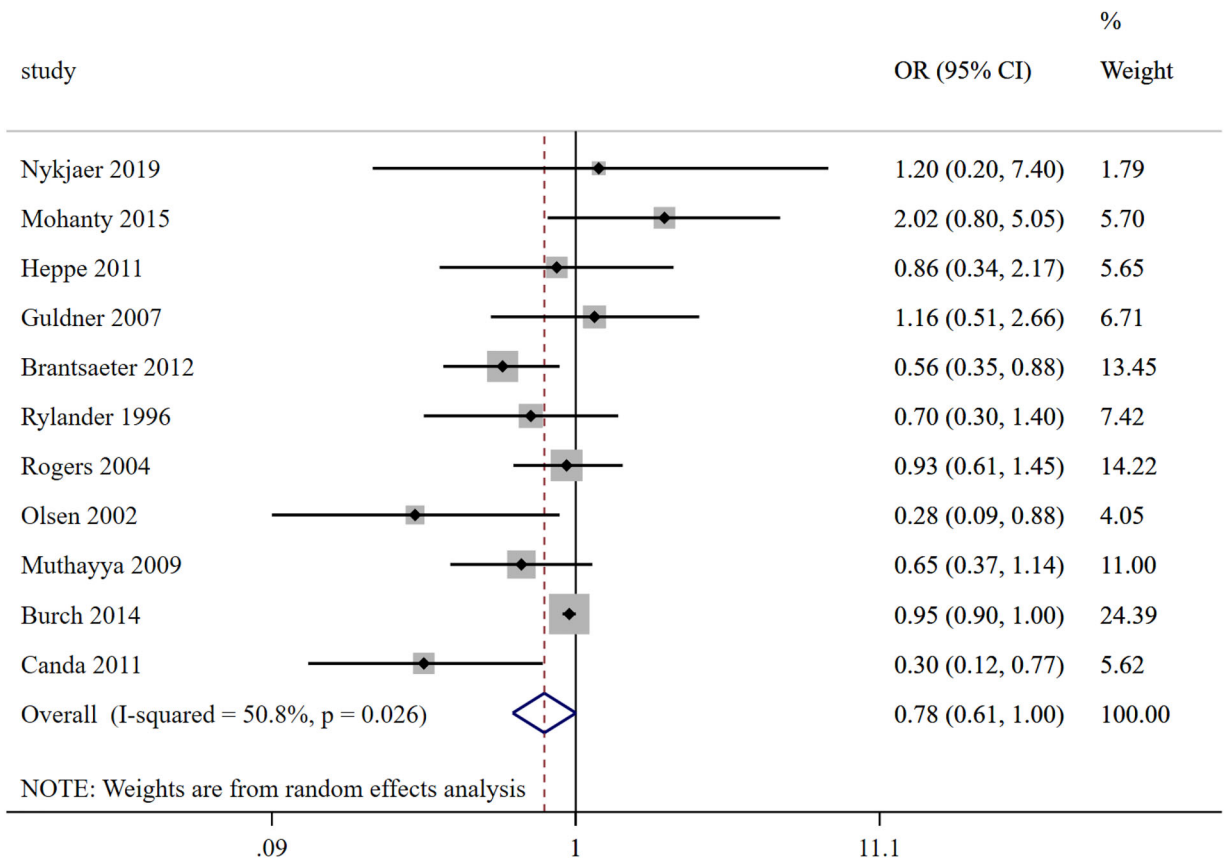

Figure 2. Maternal seafood consumption and LBW, the highest versus lowest category.

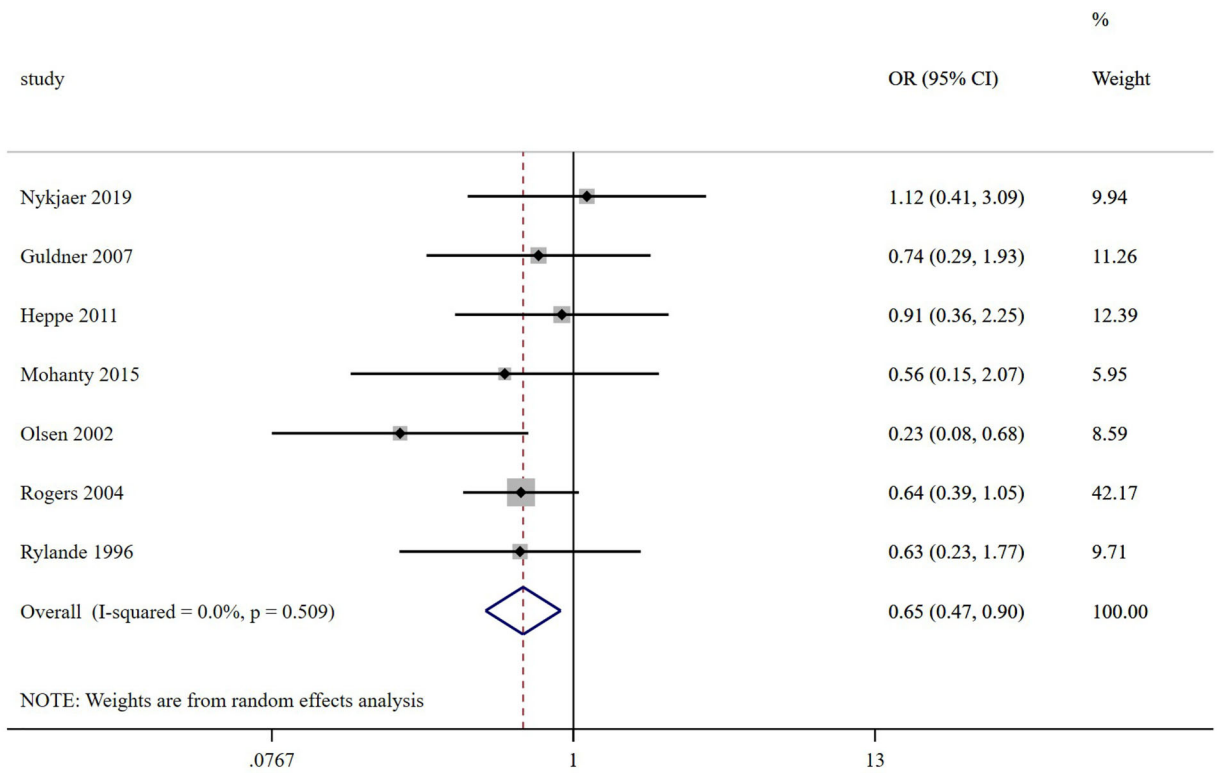

Figure 3. Linear dose-response meta-analysis for per 45 g/day increment of seafood consumption and risk of LBW.

2007; Heppe et al. 2011; Mohanty et al. 2016; Nykjaer et al. 2019; Olsen and Secher 2002; Rogers et al. 2004) were included in the dose-response meta-analysis with a total of 87625 participants and 4675 cases. The summary OR for each 45 g/day increase in seafood consumption was 0.84 (95% CI: 0.70 to 1.01) with moderate heterogeneity

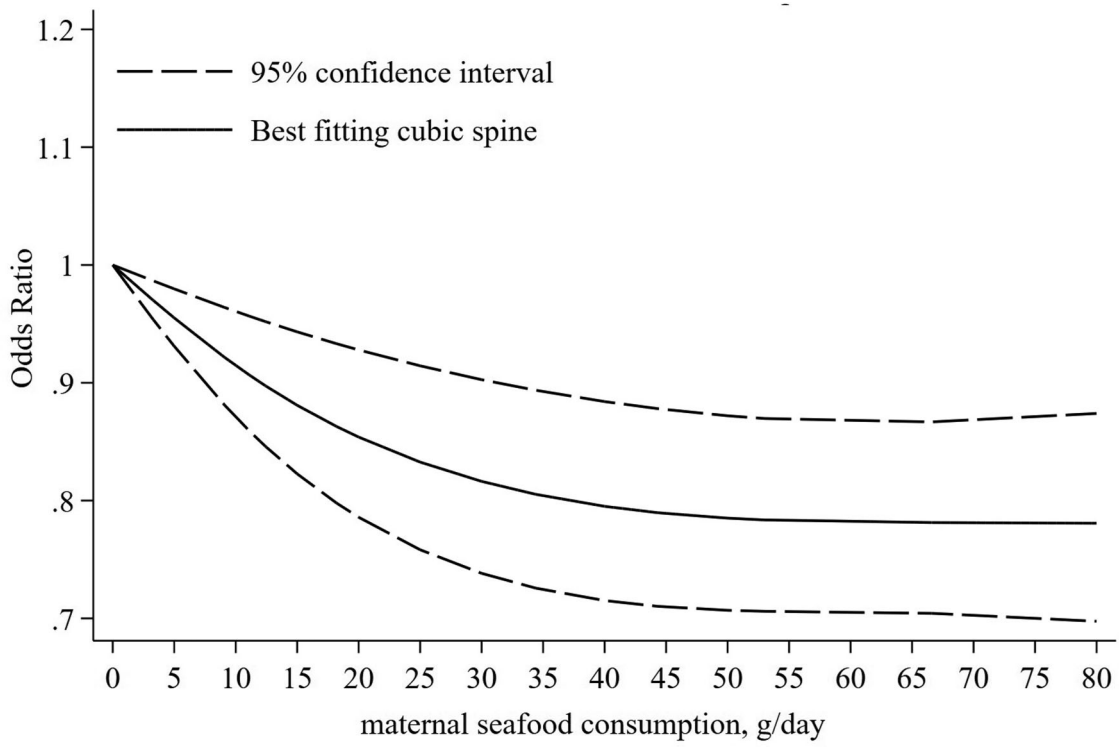

Figure 4. Non-linear dose-response association between seafood consumption and risk of PTB ($P_{\text{non-linearity}}$=0.01).

(I^2=44.6%, $P_{\text{heterogeneity}}$=0.09) (see Table 2, Supplemetry material Figure S3 in Appendix 3). Figure 4 shows the results of non-linear dose-response analysis, the risk of PTB decreased along with the increase of seafood consumption, with no further reduction in risk beyond 45 g/day intake of seafood ($P_{\text{non-linearity}}$ =0.01).

Total seafood consumption during pregnancy and the risk of SGA

Nine studies (Amezcua-Prieto et al. 2018; Canda, Sezer, and Demir 2011; Guldner et al. 2007; Halldorsson et al. 2007; Heppe et al. 2011; Mendez et al. 2010; Mitchell et al. 2004; Nykjaer et al. 2019; Ricci et al. 2010) were included in the meta-analysis on the relationship between the highest versus lowest category of maternal seafood consumption and risk of SGA, with a total of 57190 participants and 2146 cases. The pooled OR was 0.79 (95% CI: 0.59 to 1.06), with a significant between-study heterogeneity (I^2=73.2%, $P_{\text{heterogeneity}}$<0.001) (see Table 2, Supplemetry material Figure S4 in Appendix 3).

For the dose-response meta-analysis, one study (Canda, Sezer, and Demir 2011) was excluded because of dividing seafood consumption only into two categories, and one study (Halldorsson et al. 2007) not reporting the number of cases. Seven studies (Amezcua-Prieto et al. 2018; Guldner et al. 2007; Heppe et al. 2011; Mendez et al. 2010; Mitchell et al. 2004; Nykjaer et al. 2019; Ricci et al. 2010) were included in the analysis with a total of 7715 participants and 1360 cases. In terms of linear dose-response analysis, each 45 g/day increase of seafood consumption was associated with a 16% reduced risk of SGA (OR: 0.84, 95% CI: 0.71 to 0.98) with moderate between-study heterogeneity (I^2=53.7%, P = 0.04; see Figure 5, Table 2). There was no evidence of non-linearity for the relationship between maternal seafood consumption and the risk of SGA ($P_{\text{non-linearity}}$ =0.20) (see Supplemetry material Figure S5 in Appendix 3).

Subtypes of seafood consumption and the risk of adverse birth outcomes

We summarized the ORs for different subtypes of seafood, including lean fish, fatty fish and shellfish (see Table 2). There was no significant association of subtypes of seafood consumption with LBW, PTB, and SGA for the highest versus lowest category (see Supplemetry material Figure S6–S8 in Appendix 3).

A significant non-linear association was found between maternal fatty fish intake and the risk of PTB ($P_{\text{non-linearity}}$ =0.01). The risk of PTB decreased from 0 to 30 g of fatty fish per day, but began to increase when intake was above 30 g/day (see Figure 6). The linear dose-response analysis yielded that an increment of 45 g/day lean fish was positively related to LBW risk (OR: 3.51, 95% CI: 1.16 to 10.66) (see Table 2). However, the results, which only included two studies, were of low statistical power, so the findings need to be interpreted with caution.

Subgroup analysis and Meta-regression

Table 3 summarized the different subgroup analyses for the highest versus lowest category between maternal seafood consumption and perinatal outcomes. For LBW, subgroup analyses found a significant inverse association for studies

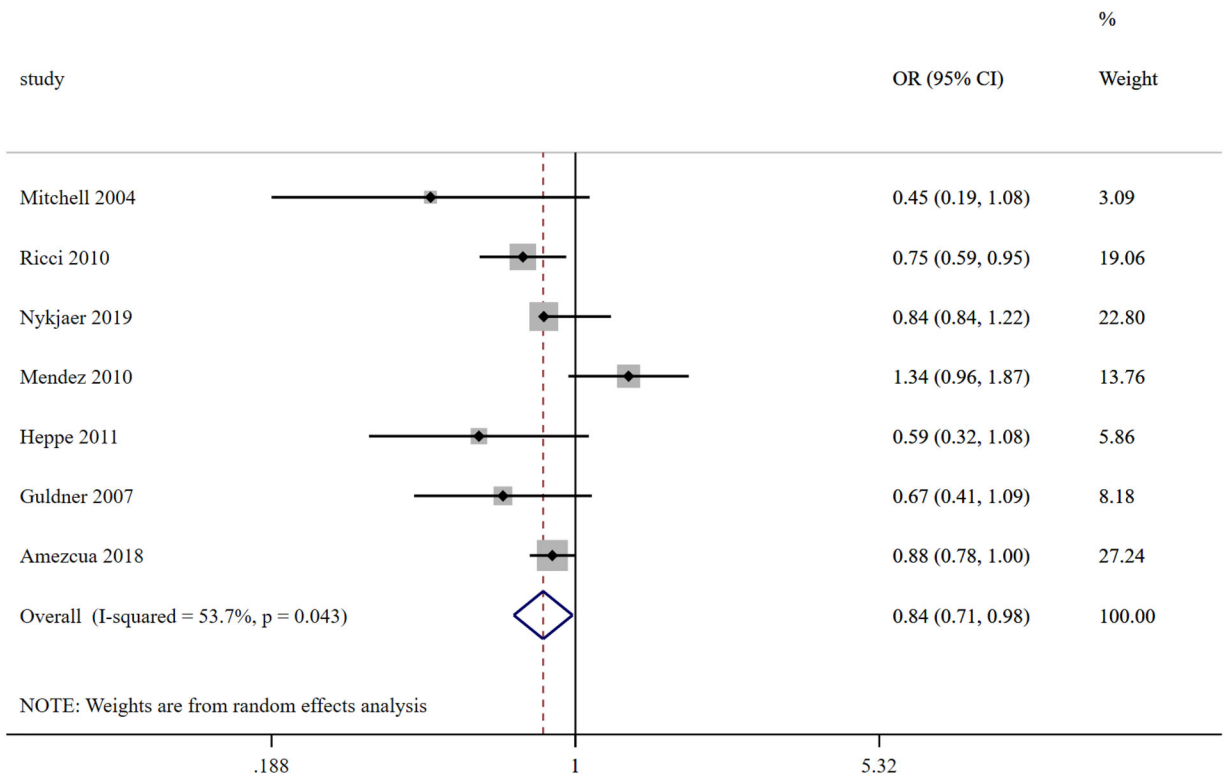

Figure 5. Linear dose-response meta-analysis for per 45 g/day increment of seafood consumption and risk of SGA.

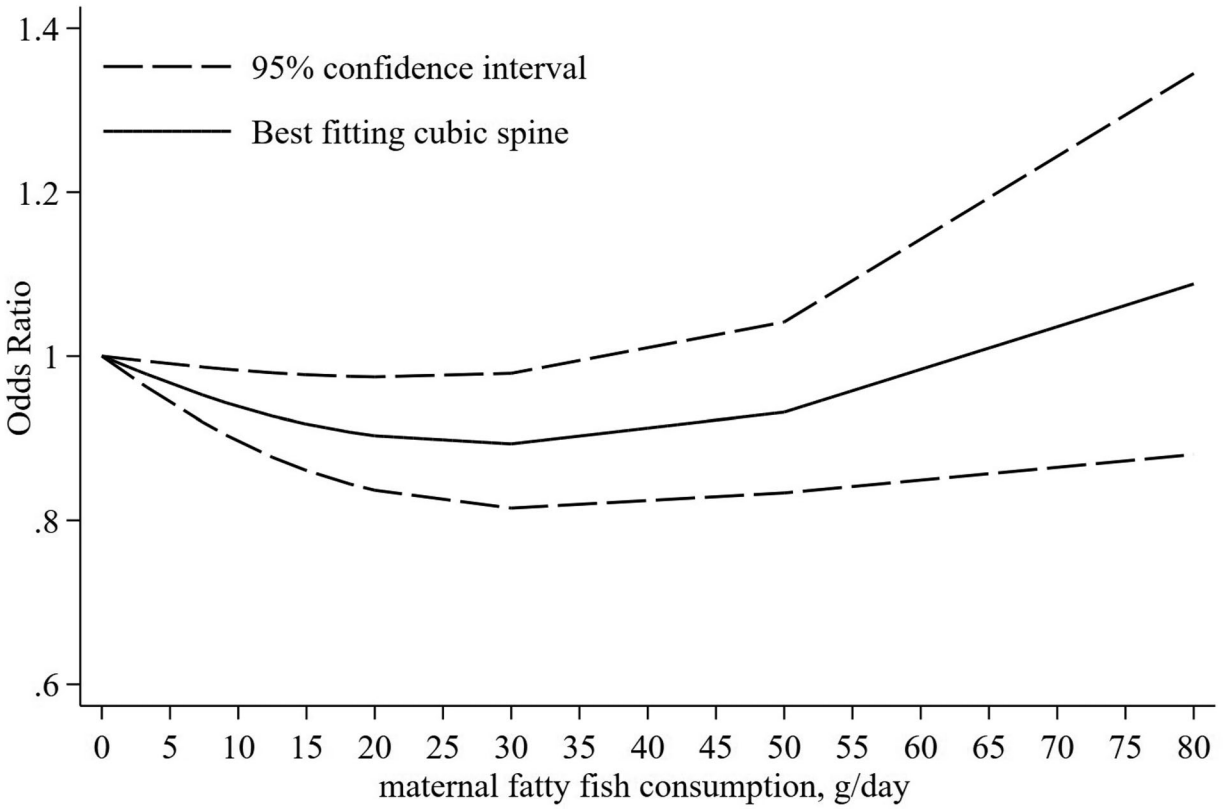

Figure 6. Non-linear dose-response association between fatty fish consumption and risk of PTB ($P_{\text{non-linearity}}$=0.01).

among Europe, and studies with no adjustment for age or maternal alcohol consumption. Furthermore, after conducting a subgroup analysis according to fish oil, there was a stronger inverse association between maternal seafood consumption and risk of LBW (OR: 0.67, 95% CI: 0.48 to 0.93) in the subgroup that adjusted fish oil supplements or excluded fish oil users. For PTB, except for the subgroup without adjustment for maternal age, most of the subgroups

followed the overall trend and showed no significant association. For SGA, we found a reduced risk of SGA in studies with case-control design, lower NOS score (<7), and a small number of participants (<3000), as well as with no adjustment for maternal age, BMI, energy intake, and fish oil. However, meta-regression analyses indicated that none of the confounding factors used was a significant contributor to the observed heterogeneity (all test $P > 0.05$).

Sensitivity analysis and publication bias

To test whether any single study would affect the pooled OR, we conducted sensitivity analyses by excluding each study in turn and the overall results were not substantially altered, with pooled ORs and 95% CIs ranging from 0.73 (0.54 to 1.00) to 0.83 (0.67 to 1.04) for LBW, 0.85 (0.67 to 1.08) to 0.96 (0.75 to 1.23) for PTB, and 0.73 (0.56 to 0.94) to 0.86 (0.66 to 1.12) for SGA (see Supplemetry material Figure S9–S11 in Appendix 3). In a further sensitivity analysis, exclusion of low-quality studies did not markedly change the significance or direction of the overall risk estimates, but reduced the heterogeneity between studies (data not shown). Additionally, in order to observe the impact of multivariable adjustment, we conducted additional sensitivity analyses by excluding studies that did not control for any confounding factors, which did not lead to any change of the results (data not shown). Begg's and Egger's tests for LBW, PTB and SGA suggested no evidence of publication bias (all test $P > 0.05$). No evidence of asymmetry was observed in funnel plots (see Supplemetry material Figure S12–S14 in Appendix 3).

Discussion

To the best of our knowledge, this is the first dose-response meta-analysis to quantify the associations between maternal seafood consumption and perinatal outcomes. Our linear dose-response analysis suggested that a 45 g increment per day of seafood intake was associated with a 35% lower risk of LBW and 16% lower risk of SGA, respectively. In addition, we found a significant non-linear dose-response relationship, in which the risk of PTB gradually decreased with the increment of seafood intake, and the risk of PTB reached the lowest point at 45 g/day, reducing the risk by approximately 30%. Furthermore, we investigated the relationship between different subtypes of seafood and perinatal outcomes, a modest J-shaped association was found between fatty fish consumption and the risk of PTB, and the lowest risk was observed at 30 g/day.

The negative association between seafood consumption and PTB observed in our results is in line with the previous meta-analysis (Leventakou et al. 2014) that reported the moderate seafood intake during pregnancy was associated with 13% lower risk of PTB. However, the results of that meta-analysis only included European cohort studies, and several prospective cohort studies conducted in other regions found inconsistent results (Mohanty et al. 2016; Mohanty et al. 2015; Muthayya et al. 2009). Moreover, more evidence has been issued since 2014, with many prospective studies showing different effects on perinatal outcomes (Amezcua-Prieto et al. 2018; Brantsaeter et al. 2017; Nykjaer et al. 2019; Smid et al. 2019). More importantly, our meta-analysis also found the linear inverse associations between seafood intakes and LBW and SGA risk, which suggested that total seafood consumption, in general, might be beneficial to perinatal outcomes.

The biological mechanisms through which seafood may potentially reduce the risk of adverse birth outcomes are not fully understood. Seafood is the main sources of n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFAs), and intervention studies with the intake of n-3 LCPUFA supplements have suggested that supplementing pregnant women with n-3 LCPUFA could prolong gestation and increase birth weight (Carlson et al. 2013; Vinding et al. 2019). It was proposed that dietary n-3 LCPUFA could affect the synthesis of bioactive molecules such as prostaglandins (PGs) (Olsen et al. 1986), which in turn influenced an array of biological activities including vasodilation, placental blood flow, cervical ripening, and the onset of labor (Imhoff-Kunsch et al. 2012). Besides, seafood is rich in other essential nutrients, including protein, iodine and vitamin D, which are also crucial on perinatal outcomes (Chen et al. 2018; Maugeri et al. 2019; Tao et al. 2018).

Different subtypes of seafood are various in nutritional components. Thus, it is necessary to consider the effect of seafood subtypes on the risk of adverse birth outcomes. Fatty fish have a higher content of n-3 fatty acids; however, observational studies on the association between fatty fish consumption and perinatal outcomes have been controversial (Halldorsson et al. 2007; Heppe et al. 2011; Mohanty et al. 2015; Nykjaer et al. 2019). Recent researches on fatty fish showed no association with PTB (Nykjaer et al. 2019), and higher intake even could be associated with reduced fetal growth (Halldorsson et al. 2007). In the current study, we found a significant J-shaped relationship between fatty fish intake and PTB risk. The lowest risk of PTB was observed with the consumption of 30 g/day (equal to 210 g/week), which is in line with the dietary recommendations in the UK (NHS Choices 2017) and Iceland (Safefood 2019). Furthermore, our linear dose-response analysis found that a 45 g/day increment of lean fish intake was positively associated with the risk of LBW. One possible explanation is that different subtypes of seafood have different cooking methods. In general, fried fish are mainly lean fish rather than fatty or shellfish (Mohanty et al. 2015), and there is evidence that dietary trans fatty acids, which are commonly used in frying, are associated with lower birth weight (van Eijsden et al. 2008). Another possible reason may be that lean fish are related to higher methyl mercury (MeHg) exposure, which have been found previously associated with LBW (Ramón et al. 2009). However, the results in lean fish are worth further discussion since only two studies were included in the analyses.

There were significant differences in subgroup analysis of geographical location. Our results identified the protective effect of seafood consumption on LBW among studies in

Europe, but not in the US or Asia. The probable explanation for the results is that the amounts of seafood consumption vary from country to country. Some studies (Brantsaeter et al. 2017; Guldner et al. 2007; Thorsdottir et al. 2004) reported that pregnant women in European countries consume about 33–43 g of seafood per day, much higher than the median intake reported in the United States (about 24 g/day) (Mohanty et al. 2016) and India (about 4 g/day) (Muthayya et al. 2009). In addition, people in different areas may eat different subtypes of seafood. A cross-sectional study indicated that there was a significant geographical difference in seafood subtypes of European countries (Welch et al. 2002). However, the findings regarding the Americas and Asia should be interpreted with caution, as our study included only a very limited number of studies in these regions.

In addition, the studies included in our meta-analysis were also heterogeneous regarding study type, sample size, study quality and adjustment of confounding factors. We also did subgroup analyses by total energy intake, sociodemographic characteristics (e.g. maternal age, pre-BMI, and education) and some lifestyles (e.g. maternal smoking status and alcohol intake) in our study, and results were in accord with the overall results with adjustment of these factors. In order to investigate the confounding effect of intake of fish oil on birth outcomes, we did the subgroup analysis according to whether fish oil was adjusted or not. We found an inverse association between seafood consumption and LBW among studies that adjusted for fish oil or excluded women who took fish oil during pregnancy, which indicated that the association observed may be influenced by residual confounding of fish oil.

Our analysis has several strengths. Firstly, we systematically searched multiple online databases to identify relevant studies. In general, compared with the previous meta-analysis, the present study included more participants, and provided updated information to clarify the relationships. Secondly, we used the risk estimates from the fully adjusted models of each study in our pooled analyses to reduce the potential influence of confounding factors. Thirdly, we got a regional difference in the association between seafood consumption and the risk of adverse birth outcomes. Fourthly, we assessed the association between perinatal outcomes with different subtypes of seafood, and also explored the dose-response relationship between subtypes of seafood and the risk based on the current evidence.

However, there are several limitations of this meta-analysis. Firstly, the limitations of observational studies include the influence of uncontrolled or residual confounders. Although we performed a great variety of relevant subgroups to explore the potential heterogeneity, the results did not identify the main source of between-study heterogeneity, which might be influenced by other dietary factors or residual confounders. For example, higher seafood consumption might be related to a healthier lifestyle, and the studies we included cannot completely rule out the residual confounding of other healthy lifestyles such as physical exercise. Secondly, all studies used food frequency questionnaires to assess the dietary intake, thus measurement error in the assessment of seafood consumption was inevitable. The imprecise measurement of consumption might lead to the attenuation of the true associations. Thirdly, only a limited number of studies have provided specific risk estimates for subtypes of seafood. Therefore, further studies should try to clarify the associations between specific subtypes of seafood and perinatal outcomes. Fourthly, most of the articles included in our study were conducted in developed regions such as Europe and North America, whereas seafood consumption varied by geographical locations and available data in developing countries was quite limited. Therefore, more prospective cohort studies are needed in developing countries, particularly in Asian countries. In addition, the cooking methods of seafood may also have an impact on birth outcomes, but this factor was not well investigated in the current original researches. Lastly, few numbers of studies were incorporated into the dose-response meta-analysis since many studies possessed only two seafood consumption categories or did not provide participants and number of cases for each category, and subgroup and meta-regression analyses were not conduced in the dose-response meta-analysis. Thus, more large-scale prospective studies with detailed information are required for the dose-response meta-analysis on the association between seafood intake and perinatal outcomes in the future.

In conclusion, our results indicate that higher consumption of seafood during pregnancy is associated with a reduced risk of LBW and SGA. There is also a non-linear association between maternal seafood consumption and risk of PTB, and the risk decreased along with the increase of seafood consumption with no further reduction beyond 45 grams per day. Moreover, the results of the different seafood subtypes in this study show that moderate intake of fatty fish during pregnancy could reduce the risk of PTB, but no more than 30 grams per day. Our findings would be useful for pregnant women to prevent adverse birth outcomes.

Future studies should pay more attention to the independent effects of different subtypes of seafood on perinatal outcomes, as well as consider the confounding effects of taking fish oil on the relationships. In addition, more studies in Asia and the Americas are needed to provide a new field for investigating the influence of region-related factors on the association between seafood consumption and perinatal outcomes.

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Authors' contribution

ZR, QG, and LH designed the study; ZR, SW researched the databases; ZR, SW collected data; ZR, QG analyzed the data; ZR drafted the manuscript; QG, LH reviewed/edited the manuscript and contributed to the discussion. All authors approved the final manuscript for submission.

Disclosure statement

The authors declared no conflict of interest.

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