Early-life high-dose omega-3 polyunsaturated fatty acid supplementation reducesrisk of childhood asthma/wheezing: A meta-analysis of randomized controlled trials

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ABSTRACT

Background and Objectives: Asthma, a chronic inflammatory airway disease characterized by wheezing, imposes a substantial global health burden on children. Given the potential of early-life omega-3 polyunsaturated fatty acid (omega-3 PUFA) supplementation—as an anti-inflammatory intervention—to prevent childhood asthma and wheezing, this meta-analysis aims to clarify its efficacy and investigate dose-dependency. **Methods and Study Design:** This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Three reviewers independently evaluated the studies, extracted data, and assessed bias using the Jadad scale. The outcomes included the risk of asthma/wheezing: pooled odds ratios (ORs) were calculated using fixed-effects models, along with sensitivity/subgroup analyses and dose-response meta-regression. **Results:** Twelve randomized controlled trials (RCTs) involving 4,156 participants showed no overall association between omega-3 PUFA and a reduced risk of asthma/wheezing (odds ratio [OR]: 1.00; 95% confidence interval [CI]: 0.84-1.18). However, high-dose supplementation (≥ 1,200 mg/day) significantly decreased the risk (OR: 0.66; 95% CI: 0.46-0.94). Similarly, high-dose eicosapentaenoic acid (EPA ≥ 1,000 mg/day) also significantly reduced the risk (OR: 0.67; 95% CI: 0.46-0.97). Dose-response analysis confirmed a linear relationship (p = 0.002), indicating a 26.6% reduction in risk for every 1,000 mg/day increase in dose (OR: 0.734; 95% CI: 0.602-0.896). Subgroup analyses revealed no heterogeneity with respect to study location, allergy risk, or follow-up duration. **Conclusions:** Early-life omega-3 PUFA supplementation reduces childhood asthma/wheezing risk in a dose-dependent manner. High-dose regimens, particularly those involving EPA, provide substantial protection, suggesting a potential clinical strategy for prevention, although further validation is required.

Key Words: omega-3 polyunsaturated fatty acid, asthma or wheezing, early-life, meta-analysis, dose-response relationship

INTRODUCTION

Asthma ranks among the most prevalent chronic conditions affecting children worldwide,[1] defined as a heterogeneous allergic inflammatory airway disease driven by multiple pathogenic mechanisms.[2] According to the Global Asthma Report, the current asthma prevalence rate of childhood asthma is 9.1%, for adolescents it is 11.0%, and for adults it is 6.6%.[3] The global prevalence of asthma has risen from 238 million cases in 2005 to 260 million in 2021.[4] It is notable that the global asthma prevalence rate is highest among children aged 5 to 9, with approximately 37.3 million children affected by the disease.[5] This disease imposes a significant burden on health and the economy, especially in severe cases, where direct medical expenses and indirect productivity losses due to home care are the most notable.[6] This has made asthma prevention and treatment a key focus of global children's health efforts.[7, 8]

The early life stage encompasses the fetal stage and the first two years after birth, a period of rapid growth and development. Bush et al. believe that this window is crucial for the maturation of the lungs and immune system, indicating that the origins of childhood asthma might be attributed to early environmental exposures.[9] In recent years, nutritional intervention during early life stage has received widespread attention as a primary prevention strategy for childhood allergic diseases.[10, 11] Particular interesting is the omega-3 polyunsaturated fatty acid (omega-3 PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are the main components of fish oil supplements.[12] These omega-3 PUFA regulate immune and inflammatory responses by competitively inhibiting arachidonic acid metabolism, thereby reducing the production of pro-inflammatory mediators such as leukotriene B_4 and prostaglandin E_2, while promoting the synthesis of inflammation-resolving mediators, including resolvins and maresins.[13]

Observational studies and clinical trials have shown that supplementation with omega-3 PUFA during pregnancy or infancy may reduce the risk of children developing asthma and wheezing. There is evidence supporting this view. Bisgaard et al. found that pregnant women who supplemented with 2.4 g of fish oil daily throughout pregnancy significantly reduced the risk of their offspring developing asthma or persistent wheezing.[14] Moreover, a 16-year longitudinal study reported that supplementing with omega-3 PUFA during pregnancy reduced the likelihood of adolescents developing asthma.[15] Despite these encouraging findings, it must be said that the current research conclusions are not consistent. It is worth noting that Tolér et al. found that supplementing with omega-3 polyunsaturated fatty acids during the preschool stage had no significant protective effect in preventing childhood

asthma/asthma-like symptoms.[16] These different results may be explained by a variety of factors, including differences in supplement dosage, the timing of the intervention, the duration of follow-up, the baseline nutritional status, and genetic susceptibility, etc..[17]

Growing evidence indicates that the health benefits of omega-3 PUFA are dose-dependent. Jager et al. emphasized this concept in a review published in 2025, stating that the Western diet typically fails to provide sufficient amounts of such fatty acids. The authors suggested that high-dose supplementation (≥ 2 g of EPA and DHA per day) might help prevent chronic lung diseases.[18] Therefore, determining the specific dose-response relationship is crucial for developing effective and targeted nutritional intervention measures.

Although some meta-analyses explore the association between omega-3 PUFA supplementation and the risk of asthma, there is a lack of meta-analyses specifically targeting early-life interventions and their dose-response relationships. Therefore, this study, through systematic searches and meta-analyses, comprehensively evaluated the impact of omega-3 PUFA supplementation during early life on the risk of childhood asthma and wheezing. Additionally, this study also explored the dose-response relationship to provide guidance for future clinical practice and evidence-based public health policies.

MATERIALS AND METHODS

The protocol for this systematic review and meta-analysis was registered with PROSPERO (registration number CRD420251157129). This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, and using methods stated in the Cochrane Handbook for Systematic Reviews of Interventions.

Literature search strategy

This research adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] A systematic search was conducted in PubMed, Web of Science, Embase, and the Cochrane Library. The retrieval period spanned from the establishment of the library until February 2026. Relevant publications were searched using specific search criteria for each database, based on the PubMed search criteria. The search strategy employed a combination of subject terms and free words. The search terms were as follows: ((fatty acids, omega 3) OR ((eicosapentaenoic acid) OR (docosahexaenoic acids) OR (alpha linolenic acid) OR (fish) OR (fish oils) OR (n 3 fatty acid*) OR (omega 3 fatty acid*) OR (n 3 oil*) OR (n 3 polyunsaturated fatty acid) OR (n 3 PUFA) OR (DHA) OR (EPA) OR (Icosapent) OR (timnodonic acid) OR (eicosapenta*noic acid) OR (docosahex*enoic acid*)

OR (docosahexaenoate) OR (linolenate) OR (linolenic acid))) AND ((asthma) OR ((asthma*) OR (bronchial asthma) OR (wheeze) OR (wheezing) OR (immunoglobulin E mediated hypersensitivity) OR (atopic) OR (allergic))) AND ((child) OR (infant) OR (adolescent) OR (pediatrics) OR (adult) OR (aged) OR (pregnancy) OR ((lactation) OR (breast feeding)) OR ((children) OR (adolescence) OR (youth*) OR (teen*) OR (teenager*) OR (elderly) OR (offspring) OR (older) OR (pregnancies) OR (gestation) OR (milk secretion) OR (prolonged lactation) OR (gestational) OR (prenatal) OR (antenatal) OR (perinatal) OR (mother*) OR (maternal) OR (pregnant))).

Inclusion and exclusion criteria

The systematic search was formulated using the PICOS framework, as were the inclusion and exclusion criteria, which are presented in Table 1.

Inclusion criteria: (1) the study design was randomized controlled trial (RCT); (2) the participants were pregnant women and their children; (3) in the experimental group, omega-3 polyunsaturated fatty acid supplements (in any form) are provided during the early life stage, while in the control group, a placebo (such as olive oil, soybean oil, or vegetable oil) is given; (4) the outcome indicators are the reported prevalence of asthma/wheezing.

Exclusion criteria: (1) studies lacking dose and outcome data, or studies from which such data cannot be obtained; (2) studies with incomplete outcome data; (3) for studies involving multiple research groups and with overlapping research subjects, except for the group with the longest follow-up period, the other groups were excluded; (4) duplicate publications; (5) non-English literature.

Outcome measures

In this study, the primary outcome indicator was the prevalence of asthma/wheezing, which was defined as clinical diagnosis, parental report of asthma symptoms, at least three episodes of wheezing in the past two years, or parental report of a physician's diagnosis of asthma.

Data extraction and quality assessment

The data extraction was independently completed by three investigators. To ensure accuracy, cross-checking was conducted. In case of any discrepancies, they were resolved through consensus discussion or arbitration by other investigators. The following parameters were systematically collected: (1) baseline study characteristics (first author, publication year, country, and study design); (2) participant demographic information (sample size and

population characteristics); (3) details of the intervention measures (types, doses, supplementation timing, and duration of omega-3 PUFA); (4) outcome indicators (definitions of asthma/wheezing and follow-up duration); and (5) variables related to bias risk assessment. The methodological quality was evaluated using the Jadad scale.[20] This scale assesses key aspects such as random sequence generation, allocation concealment, use of blinding, and withdrawal handling. The studies were classified into two categories: low-quality (score: 1-3 points) or high-quality (score: 4-7 points). All 12 included RCTs received a high-quality rating.

Statistical analysis

The effect size was presented in the form of odds ratio (OR) and its 95% confidence interval (CI). These data were calculated based on the number of events and the total number of included studies. Additionally, I^2 was used to quantify the potential variability among the included studies. When the heterogeneity was not significant ($I^2 < 50\%$), a fixed-effect model was used to summarize the results. When the heterogeneity was significant ($I^2 > 50\%$), a random-effects model was used for meta-analysis.[21] The publication bias was evaluated through funnel plots and Peters' test. Sensitivity analysis was conducted to assess the robustness of the results. After sequentially excluding each study, the pooled effect size OR was recalculated. A single-stage random-effects meta-regression model was used to estimate the dose-response relationship, and the restricted maximum likelihood (REML) method was applied to estimate the remaining heterogeneity. All statistical analyses were carried out using R software (version 4.5.1), and packages such as meta, metafor, dosresmeta, tidyverse, and ggplot2 were used.

RESULTS

Literature screening process and research characteristics

In accordance with the PRISMA guidelines,[19] a systematic search was conducted on PubMed, Medline, Web of Science, Embase, and the Cochrane Library. Initially, 7,573 records were obtained. After removing duplicates, 4,550 records were finally obtained. Subsequently, the titles and abstracts were screened, and 4,476 records were excluded. The remaining 74 full-text articles were used for in-depth assessment. During the full-text evaluation process, 62 articles were further excluded due to non-RCT design, mismatched intervention type, lack of pre-defined outcome indicators, irrelevant study subjects, or duplicate publication. Finally, 12

RCTs were included in this meta-analysis. The flowchart of the study selection process and the progress of RCTs are shown in Figure 1.

Study characteristics

Overall, a total of 12 RCTs were included, involving a total of 4,156 participants (Supplementary Table 1).[16, 22-29] The study by Berman et al. contributed two independent datasets to the meta-analysis, as it evaluated two different intervention formulations (EPA-rich and DHA-rich fish oil) against a single placebo.[27] Therefore, a total of 13 independent data sets were ultimately included. The studies covered multiple countries and regions. Among them, 5 studies were from Europe,[23, 26, 28, 30, 31] 2 studies were from the Americas,[24, 27] and 5 studies were from Oceania.[16, 22, 25, 29, 32] There were 7 studies on the supplementation of omega-3 PUFA during pregnancy,[22, 24, 26-30] 2 studies during lactation,[25, 32] 2 studies during both pregnancy and lactation,[23, 31] and 1 study was conducted in preschool children.[16] Among the included studies, 5 classified the offspring as "high allergy risk",[16, 22, 23, 26, 29] which was defined as having a medical diagnosis of allergic diseases in at least one first-degree relative, such as asthma, eczema, or allergic rhinitis. The other 7 studies recruited participants from the general population without such family predisposition.[24, 25, 27, 28, 30-32] The intervention dose of omega-3 PUFA ranged from 185 to 3,700 mg per day. The follow-up duration varied from 6 months to 24 years. 7 studies reported clinically diagnoses of asthma,[16, 22, 23, 28, 30-32] 8 studies reported wheezing symptoms,[16, 22, 24-26, 29, 31] and 1 study reported asthma/wheezing outcomes.[27] There were subtle differences in the definition of the primary outcome "asthma/wheezing" among the studies, including physician's diagnosis, parent's report, wheezing frequency, or IgE-related asthma. For all studies, the number of events and sample sizes of the intervention group and control group were provided to conduct a meta-analysis of effect size OR and dose-response analysis.

Meta-analysis results of trials

Pooled results from 12 RCT studies involving 4,156 infants indicated that, when compared with the control groups, fish oil supplementation was not associated with an overall reduced risk of asthma/wheezing (OR: 1.00, 95%CI: 0.84 - 1.18, I^2 = 9.7%) (Figure 2).[16, 22-28]

Subgroup analysis

The results were stratified based on study location, outcomes, the risk of allergic disease in infants, the dose (omega-3 PUFA, EPA, DHA), the timing of intervention, and follow-up

duration. As shown in Table 2, supplementation with high-dose omega-3 PUFA (≥ 1,200 mg/day) significantly decreased the risk of asthma/wheezing (OR: 0.66, 95%CI: 0.46-0.94) (Figure 3). High-dose EPA supplementation (≥ 1,000 mg/day) was associated with a significantly reduced risk of childhood asthma or wheezing (OR: 0.67, 95% CI: 0.46–0.97; Figure 4). In contrast, no such significant reduction in the risk of childhood asthma or wheezing was observed in the lower-dose subgroups (omega-3 PUFA < 1,200 mg/day or EPA < 1,000 mg/day). Factors such as study location, outcomes, infant risk of allergic disease, dose of DHA, timing of intervention, and follow-up duration had no significant effect on the risk of asthma/wheezing.

Sensitivity analysis

Sensitivity analysis showed that the combined effect size did not change significantly after excluding each study in turn (OR: 0.95-1.07, $p > 0.05$), and the results were consistent (Supplementary Figure 1).

Dose-response analysis

In this study, the linear dose-response regression analysis was performed using a one-stage random-effects meta-regression model. As illustrated in Figure 5, a consistent, linear trend was observed: supplementation with higher doses of omega-3 PUFA during early-life was positively correlated with a gradual reduction in the risk of childhood asthma/wheezing. This protective effect emerged at lower doses (e.g., 400-500 mg/day) and seemed to peak within a range of approximately 2,400-2,700 mg/day. Overall, this analysis confirmed a significant negative linear relationship between omega-3 PUFA and the risk of asthma/wheezing ($p = 0.002$). Specifically, daily supplementation of 1,000 mg omega-3 PUFA corresponded to a significant 26.6% reduction in the risk (OR: 0.734; 95% CI: 0.602-0.896).

Publication bias

The funnel plot exhibited good symmetry, and the Peters' test indicated no significant publication bias ($p = 0.614$) (Supplementary Figure 2).

DISCUSSION

In this meta-analysis of RCTs, there was no overall association between early-life supplementation with fish oil and the risk of childhood asthma/wheezing. However, subgroup analyses revealed that the high-dose regimen (total intake of omega-3 PUFA ≥ 1,200 mg/day

or EPA intake ≥ 1,000 mg/day) significantly reduced the incidence of asthma/wheezing. In contrast, low-dose supplementation did not show any protective effect. It is noteworthy that the observed benefits were not affected by the infants' allergy risk status, the timing of intervention, or follow-up duration. Similarly, Jia et al[33] based on the European cohort also pointed out that supplementing with high doses of fish oil in early life can reduce the risk of clinical asthma diagnosis. Unlike Jia et al., our meta-analysis included studies from a broader region including the Americas, Oceania, and Europe.

The dose-response analysis further showed a significant negative linear relationship within a specific dose range. Specifically, for every 1,000 mg/day increase in omega-3 PUFA intake, the risk of asthma/wheezing decreased by 26.6% (OR: 0.734; 95% CI: 0.602-0.896). Collectively, these findings suggest that early supplementation with high-dose omega-3 PUFA may provide clinical protective effects in preventing the occurrence of children asthma. Consistent with the findings of Lin et al.,[34] they reported that daily supplementation of omega-3 PUFA at a dose of ≥ 2,000 mg during pregnancy significantly reduced the risk of childhood asthma/asthmatic wheezing. Our stratified analysis, however, identified a protective effect at a lower threshold (1,200 mg per day).

In comparison to previous meta-analyses, our study has made significant improvement in methodology. First, we carried out a comprehensive literature search up to February 2026. By applying pre-defined criteria, we aimed to address potential biases that might arise from duplicate publications in overlapping cohorts. Specifically, for multiple published trials, only the data sets with the longest follow-up period and the most comprehensive reporting were included, thereby avoiding the duplicate participant data. This rigorous screening process ultimately resulted in 12 independent RCTs involving 4,156 participants. Secondly, sensitivity analysis verified the robustness of our findings; after eliminating individual studies one by one, the overall effect estimates did not show any significant change. Finally, the dose-response relationship between omega-3 polyunsaturated fatty acids and asthma/asthmatic symptoms was also analyzed. The dose-response model further confirmed the existence of a positive gradient within a specific range, indicating that the higher the intake, the more significant the protective effect. These stratified analyses enhanced the clinical significance of our research findings.

However, several limitations of this study should be acknowledged. Although the dose–response analysis confirmed a significant linear protective association between early-life omega-3 PUFA intake and the risk of childhood asthma/wheezing, the number of original studies in the high-dose subgroup was relatively limited. Therefore, the stability of the

dose-dependent conclusion needs to be further validated by future research. Moreover, this meta-analysis could not determine the optimal intervention threshold and critical window for preventing childhood asthma/wheezing. In addition, the analysis did not explore effect modification by genetic susceptibility. More large-scale, high-quality randomized controlled trials are warranted to identify the optimal regimen and support the development of personalized preventive strategies.

Notably, regarding clinical translation, the safety profile of high-dose interventions warrants careful consideration. Existing evidence from broader cardiovascular literature indicates that high-dose omega-3 PUFA intake may be associated with increased risks of atrial fibrillation, bleeding events, and gastrointestinal symptoms.[35, 36] Therefore, when implementing high-dose omega-3 PUFA intervention in the future, a careful benefit-risk assessment is required.

Conclusion

In summary, this updated meta-analysis demonstrates that high-dose fish oil supplementation (≥ 1,200 mg/day) and EPA (≥ 1,000 mg/day) during early-life period is associated with a reduced risk of asthma/wheezing, and a statistically significant dose-response relationship was observed. Low-dose supplementation did not confer a significant protective effect. This association remained robust across various subgroups and was not affected by geographical region, allergic background, intervention timing, or follow-up duration. Although high-dose supplementation may carry potential risks of adverse events, the results of this study support the exploration of the potential value of high-dose omega-3 PUFA supplementation in the primary prevention of childhood asthma. Future large-scale, long-term, and high-quality RCTs are still needed to determine the optimal dose, safety, and long-term effects, thereby providing more accurate evidence-based medical basis for individualized primary prevention of childhood asthma.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1. PICOS framework

Parameter	Criteria
Population	Included: studies where the subjects were pregnant women and their children Excluded: studies not involving pregnant women and their children
Intervention	Included: studies using omega-3 PUFA (in any form) as the intervention measure Excluded: studies that included other intervention measures and thus made it impossible to clearly determine the effect of omega-3 PUFA
Comparison	Placebo (such as olive oil, soybean oil, vegetable oil)
Outcome	The primary outcome indicator was the prevalence of asthma/wheezing, which is defined as: clinical diagnosis, parental report of asthma symptoms, at least three episodes of wheezing within the past two years, or parental report of a physician's diagnosis of asthma.
Study design	Included: Randomized controlled trials. Excluded: (1) non-RCTs; (2) studies lacking dose and quantity data, or where such data could not be obtained; (3) studies with incomplete outcome data.

PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial.

Table 2. Subgroup analysis of the included RCTs.

Subgroup classification characteristics	Risk of asthma/wheezing			
	Number of datasets	Number of subjects	OR (95% CI)	I^2 (%)
Study location				
America	3	945	1.05 (0.71, 1.54)	0.0%
Oceania	5	1,909	1.12 (0.89, 1.40)	0.0%
Europe	5	1,302	0.70 (0.49, 1.02)	0.0%
Outcomes				
Asthma	7	2,321	0.86 (0.60, 1.22)	40.0%
Wheeze	8	3,089	1.11 (0.92, 1.32)	0.0%
Asthma/wheezing	2	111	0.83 (0.35, 1.98)	0.0%
Infant risk of allergic disease				
High allergic risk†	5	1,301	1.09 (0.81, 1.46)	0.0%
Non-high allergic risk	8	2,855	0.92 (0.69, 1.23)	26.0%
Dose of fish oil				
<1,200 mg/d	7	2,796	1.13 (0.93, 1.37)	0.0%
≥1,200 mg/d	6	1,360	0.66 (0.46, 0.94)	0.0%
Dose of EPA				
<1,000 mg/d	8	3,059	1.11 (0.92, 1.35)	0.0%
≥1,000 mg/d	5	1,097	0.67 (0.46, 0.97)	0.0%
Dose of DHA				
<800 mg/d	5	1,666	1.25 (0.96, 1.64)	0.0%
≥800 mg/d	8	2,490	0.84 (0.67, 1.06)	8.4%
Timing of intervention				
Pregnancy	8	2,514	0.85(0. 67,1.08)	9.7%
Lactation	2	810	1.17 (0.85, 1.61)	0.0%
Pregnancy and lactation	2	382	0.83 (0.34, 2.05)	0.0%
Preschool period (6 months–5 years)	1	450	1.32 (0.84, 2.06)	-
Follow-up duration				
<3 years	8	1,734	1.07 (0.79, 1.43)	0.0%
≥3 years	5	2,422	0.92 (0.68, 1.25)	48.2%

OR: odds ratio; CI: confidence interval; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; I^2 is for statistical heterogeneity within studies.

† "High allergic risk" was defined as having a medical diagnosis of allergic diseases in at least one first-degree relative, such as asthma, eczema, or allergic rhinitis.

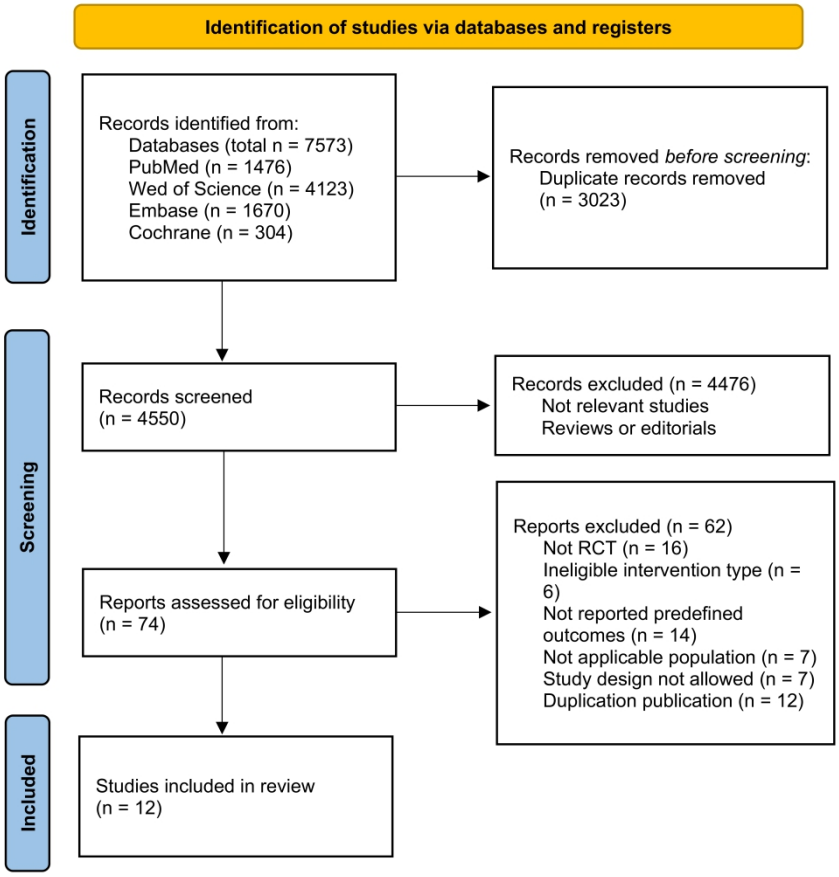

Figure 1. Prisma flow chart of the article selection process.

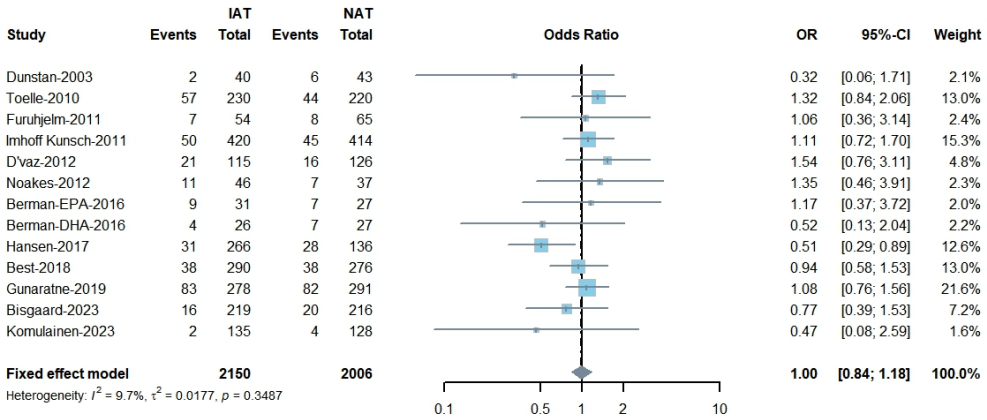

Figure 2. Forest plot of the effect of early-life supplementation with fish oil on the risk of asthma/wheezing.

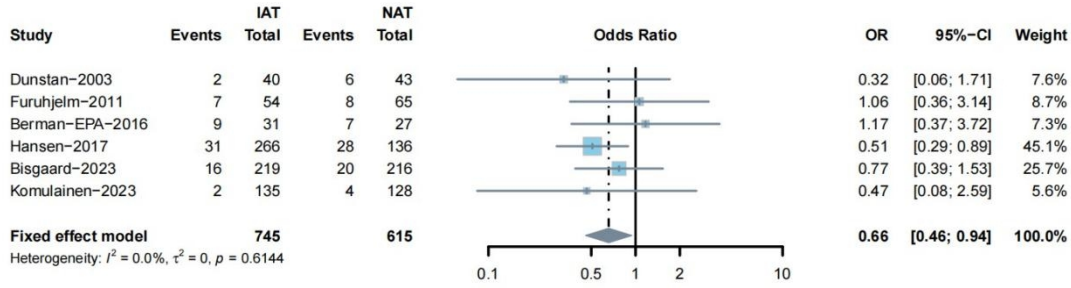

Figure 3. Forest plot of the effect of fish oil dose (≥ 1,200mg/day) on the risk of asthma/wheezing.

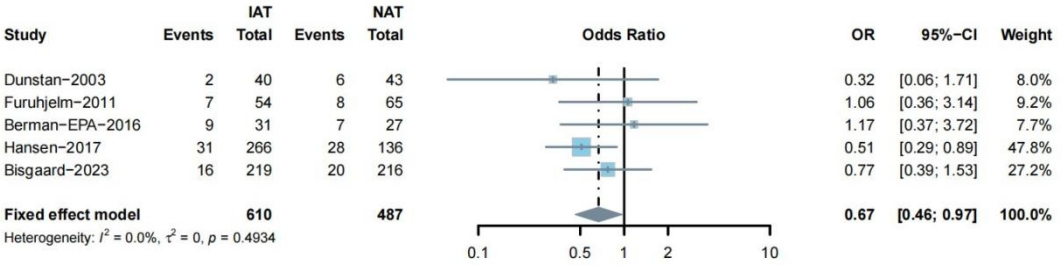

Figure 4. Forest plot of the effect of EPA dose (≥ 1,000mg/day) on the risk of asthma/wheezing.

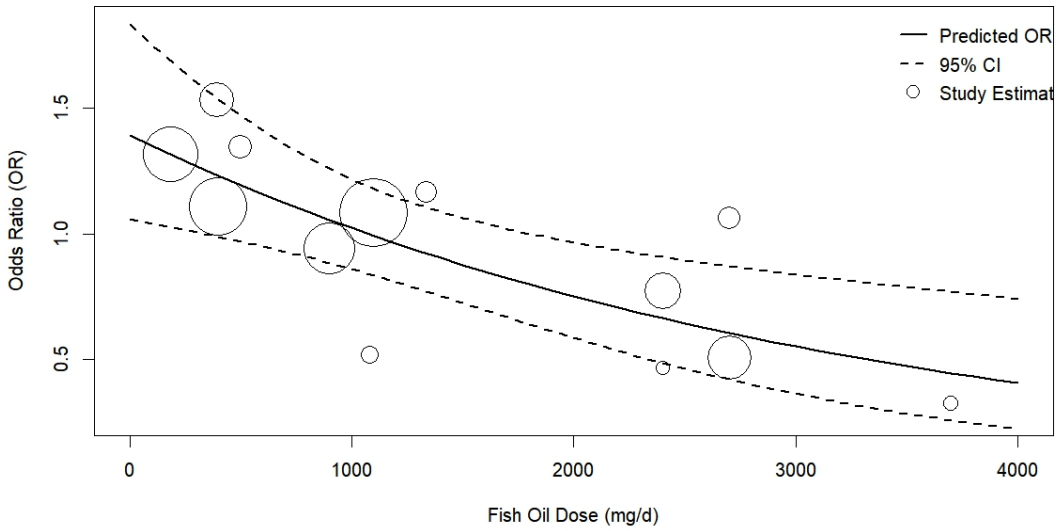

Figure 5. Dose-response meta-analysis between fish oil dose and the risk of asthma/wheezing.