Systematic Review and Meta-Analysis

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Vitamin A supplementation prevents the bronchopulmonary dysplasia in premature infants

A systematic review and meta-analysis

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Abstract

Background: It is necessary to evaluate the effectiveness and safety of vitamin A supplementation on the bronchopulmonary dysplasia (BPD) in premature infants.

Methods: Randomized controlled trials (RCTs) on the role of supplemental vitamin A in preterm infants were searched. The Medline et al databases were manually searched from inception to April 30, 2020. Related outcomes including incidence of BPD, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), sepsis and mortality were assessed with Review Manager 5.3 software, and Random-effect model was applied for all conditions.

Results: A total of 9 RCTs with 1409 patients were included. The analyzed results showed that the incidence of BPD in vitamin A group was significantly less than that of control group (OR = 0.67, 95%CI [0.52–0.88]). There was no significant difference in the incidence of ROP (OR = 0.65, 95%CI [0.29–1.48]), NEC (OR = 0.88, 95%CI [0.59–1.30]), IVH (OR = 0.90, 95%CI [0.65–1.25]), sepsis (OR = 0.84, 95%CI [0.64–1.09]) and mortality (OR = 0.98, 95%CI [0.72–1.34]) among two groups.

Conclusion: Vitamin A supplementation is beneficial to the prophylaxis of BPD in premature infants, further studies on the administration approaches and dosages of vitamin A in premature infants are warranted.

Abbreviations: BPD = bronchopulmonary dysplasia, CI = confidence interval, CNKI = China National Knowledge Infrastructure, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, OR = odd of risk, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis, RCTs = randomized controlled trials, ROP = retinopathy of prematurity.

Keywords: bronchopulmonary dysplasia, infant, premature, vitamin A

1. Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common chronic diseases of premature infants.[1] Not only does the mortality rate are high, but also the impact on surviving children may last for life, bringing a heavy burden on the children's physical and mental health, family, and society.[2] Moreover, the incidence of BPD is also increasing.[3] Scholars such as Northway first proposed the concept of BPD in 1967.[4] For more than 50 years, humans have conducted a lot of research on the prevention and treatment of BPD. Although many progresses have been made, there is currently no definite and effective treatment, and its prevention is especially important.

Many studies[5,6] have shown that vitamin A may be beneficial for the prevention of BPD. As early as 1987, a double-blind randomized controlled trial (RCT)[7] showed that supplementing vitamin A can reduce the incidence of BPD. However, recently some scholars have proposed the opposite point of view, it is believed that vitamin A is ineffective in preventing BPD and increases the risk of sepsis in children.[7] Tolia et al[8] have also founded that the neonatal death and the occurrence of BPD may not be affected by recent vitamin A deficiency. It can be seen that whether vitamin A can prevent the occurrence of BPD is still controversial. Previous meta-analyses[9,10] have compared the effects and safety of vitamin A in the premature infants, yet the results have remained inconsistent. Furthermore, the sample size is rather small. Therefore, an updated meta-analysis on the role of vitamin A in the premature infants is needed. In this present study, we aimed to comprehensively evaluate the effectiveness and safety of supplemental vitamin A in preterm infants, to provide a reference for clinical management of premature infants.

2. Methods

This systematic review and meta-analysis did not pre-registered on the website, and it was reported in following of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[11]

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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2.1. Eligibility criteria

Studies were included in this present review if following PICOS criteria were met:

1. Participants: Preterm infants (gestational age <37 weeks) without congenital abnormalities.
2. Intervention: trials that compared patients who received vitamin A vs did not receive vitamin A supplementation.
3. Outcomes: related outcomes on the effects and safety were reported, including the incidence of BPD, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), sepsis, and mortality.
4. Design: RCT, published in a peer reviewed journal.

The literature exclusion criteria were:

1. The quality of the literature was poor, including serious flaws in research design, improper random methods, etc.
2. For the same study which was published multiple times, the one with the largest sample size was taken, and others were excluded;
3. Unable to obtain the original text or not get sufficient original data for meta-synthesis

Literature search strategy

The Medline, Science Direct, Cochrane Central Register of Controlled Trials, EMBASE, China National Knowledge Infrastructure (CNKI) and Wanfang database were manually searched from inception to April 30, 2020. We used the combination of subject words and free words to perform the search process. The search terms were as follows: (vitamin A OR Vit A OR V A) AND (premature or preterm or neonate or newborn or infant or epilepsy). There were no language restrictions applied during the search process in this present study.

2.3. Data extraction

The two reviewers independently screened the literatures according to the inclusion and exclusion criteria, and used the same data extraction table to extract the data and check with each other. If there were disagreements, they were resolved through discussion or decided by the third researcher. The extracted information included:

1. The first author, the year of publication, the country, and other basic information of the included literature;
2. Research methods and key elements of RCT for the bias risk assessment;
3. interventions, including the time, route, dose, and duration of treatment course;
4. related outcomes: the incidence of BPD, ROP, NEC, IVH, sepsis, and mortality.

The assessment on the quality of included RCTs

The qualities of related RCTs were independently evaluated by two of our reviewers. And any conflicting results were further judged by another author. We used Cochrane Collaboration's tool of bias risk[12] to assess the methodological quality and potential risk of bias in the included RCTs. This tool includes seven specific domains: sequence generation, assignment hiding, blindness of participants and personnel, blindness of outcome evaluation, incomplete result data, selective result reporting, and other issues. According to the judgment criteria, each domain is classified as low bias risk, high bias risk, or unclear bias risk. Statistical analysis

All the statistical analyses were conducted using the Review Manager 5.3 software (Copenhagen). The odd of risk (OR) with related 95% confidence intervals (CI) was calculated to estimate the synthesized effects of included RCTs. Furthermore, the statistical heterogeneity was evaluated with Q-test and I^2, and the I^2 values of 25%, 50%, and 75% were taken as being lowly, moderately, and highly heterogeneous respectively. Random-effect model were applied for all conditions. Subgroup analysis based on intervention differences were conducted to ascertain the potential origin of heterogeneity. Furthermore, sensitivity analysis was performed by neglecting one study at one time and evaluating the influence of each included RCTs. For all the statistical analyses in this present meta-analysis, $P < .05$ was taken as statistical significance, and all examined tests were two-sided.

3. Results

3.1. Study selection

The selection process is presented in Figure 1. The initial search resulted in 161 potentially relevant articles. After reviewing the titles and abstracts of the remaining 104 studies after duplicate exclusion, the full text of 25 studies was retrieved. After careful and discreet evaluation based on the included and excluded criteria, 9 RCTs were included finally.

3.2. The characteristics of included RCTs

A total of 9 RCTs[7,13–20] with 1409 patients were included, of whom 709 infants received vitamin A treatment, and 700 infants did not receive vitamin A treatment. The characteristics of included RCTs were presented in Table 1. Five reported RCTs[7,15,16,18,20] were conducted in the United States, two[14,19] in England, and one in Thailand[13] and China,[17] respectively. And dose of vitamin A regimens varied from 1500 to 10,000 IU, and the treatment durations generally lasted for 4 weeks.

3.3. Literature quality evaluation

The quality of included 9 RCTs were presented in Figures 2 and 3. Although each study mentioned randomization, and four RCTs[7,14,16,20] did not mention a specific random method, and there might be pseudo-randomness. Two RCTs[17,20] did not explicitly reported the distribution and concealment or whether to use blind method. One study[20] did not report the type and number of specific adverse reactions in detail, and the remaining four studies all reported that. No other significant biases were detected.

3.4. Synthesized outcomes

The incidence of BPD Six RCTs[7,13,15,16,18,19] reported the incidence of BPD among two groups. No significant heterogeneity was found among included RCTs ($I^2 = 0\%$). The analysis result showed that the incidence of BPD in the vitamin A group was significantly less than that of control group (OR = 0.67, 95% CI [0.52–0.88], Fig. 4A).

The incidence of ROP Four RCTs[7,13,14,19] reported the incidence of ROP among two groups. No significant heterogeneity was found among included RCTs ($I^2 = 53\%$). The analysis result showed that there was no significant difference in the incidence of ROP among two groups (OR = 0.65, 95%CI [0.29–1.48], Fig. 4B).

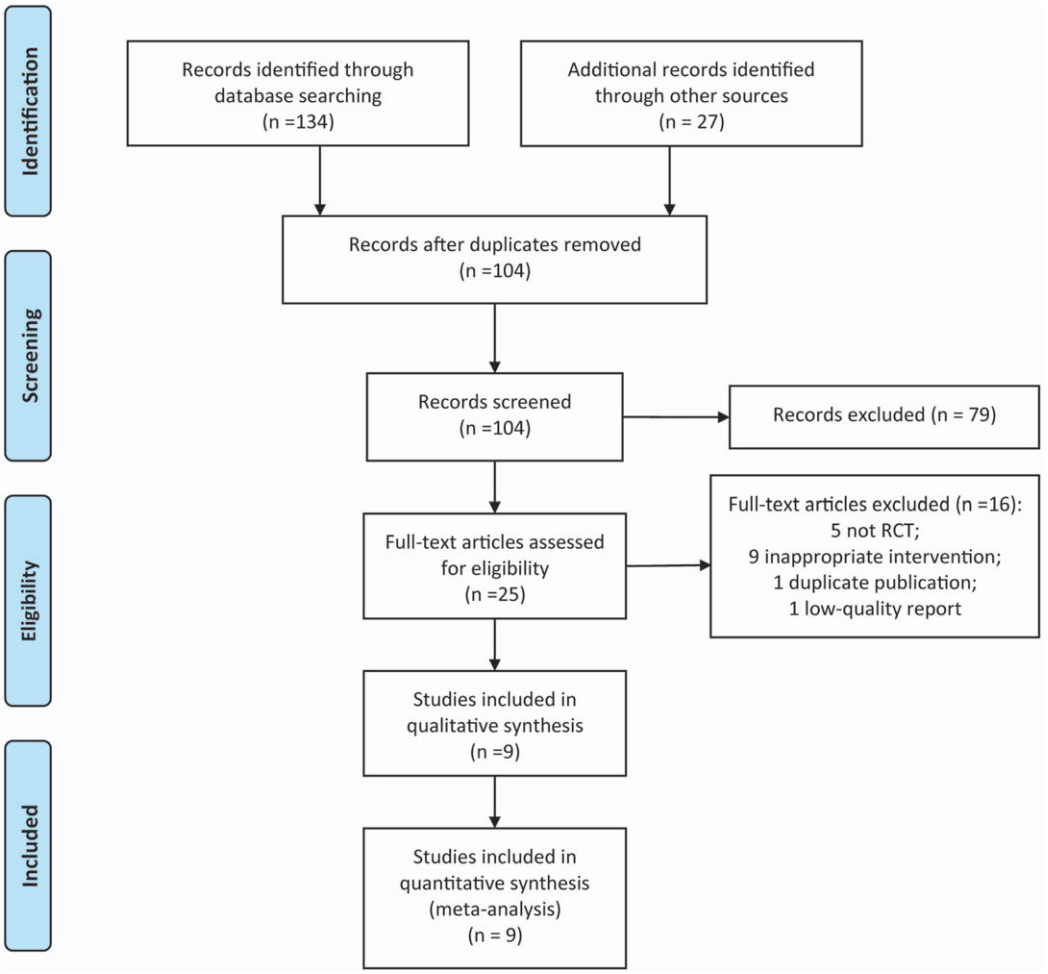

Figure 1. The flow chart of study selection.

The incidence of NEC Three RCTs[13,16,18] reported the incidence of NEC among two groups. No significant heterogeneity was found among included RCTs ($I^2=0\%$). The analysis result showed that there was no significant difference in the incidence of NEC among two groups (OR = 0.88, 95%CI [0.59–1.30], Fig. 4C).

The incidence of IVH Four RCTs[13,14,18,19] reported the incidence of IVH among two groups. No significant heterogeneity was found among included RCTs ($I^2=0\%$). The analysis result showed that there was no significant difference in the incidence of IVH among two groups (OR = 0.90, 95%CI [0.65–1.25], Fig. 4D).

The incidence of sepsis Three RCTs[13,18,19] reported the incidence of sepsis among two groups. No significant heterogeneity was found among included RCTs ($I^2=0\%$). The analysis result showed that there was no significant difference in the incidence of sepsis among two groups (OR = 0.84, 95%CI [0.64–1.09], Fig. 4E).

Table 1

The characteristics of included RCTs.

Studies	Countries	Sample (vit A/control)	Gestational age (w)	Birth weight (g)	Interventions		
					Vit A group	Control group	Frequency and duration
Kiatchoosaku 2014	Thailand	40/40	24–32	<1500	im, 5000 IU	None	3/w, 4w
Mactier 2012	England	42/47	<32	<1501	im, 10,000 IU	None	3/w, 2~4w
Pearson 1992	USA	27/22	27 ± 1	700–1100	im, 2000 IU	Normal saline	Once every other day, a total of 14 times
Ravishankar 2003	USA	22/18	<32	500–1500	im, 1500–3000 IU	None	The 1st, 3rd, 7th day after birth
Shenai 1987	USA	20/20	26–30	700–1300	im, 2000 IU	Normal saline	Once every other day, a total of 14 times
Tyson 1999	USA	405/402	<30	401–1000	im, 5000 IU	None	3/w, 4w
Wardle 2001	England	77/77	25–27	<1000	po, 2000 IU	Placebo	1/d, 28d
Werkman 1994	USA	44/42	<31	725–1300	iv gtt, 210~476 RE	None	1/d, 4w
Tang 2016	China	32/32	27–33	<1500	po, 5000 IU/kg	None	1/d, 4w

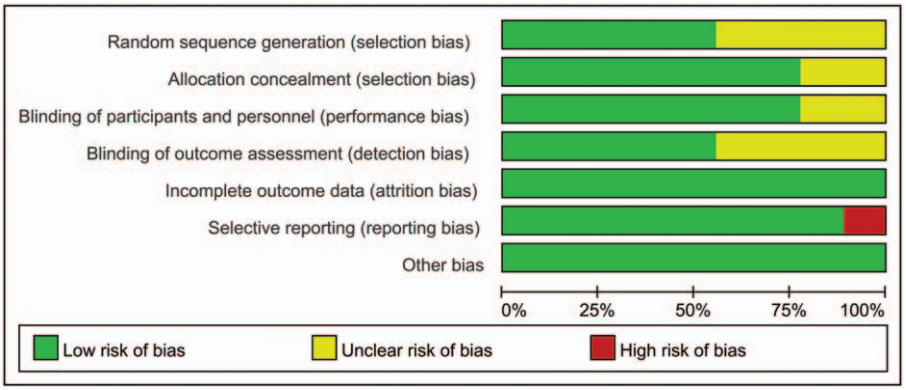

Figure 2. Risk of bias graph.

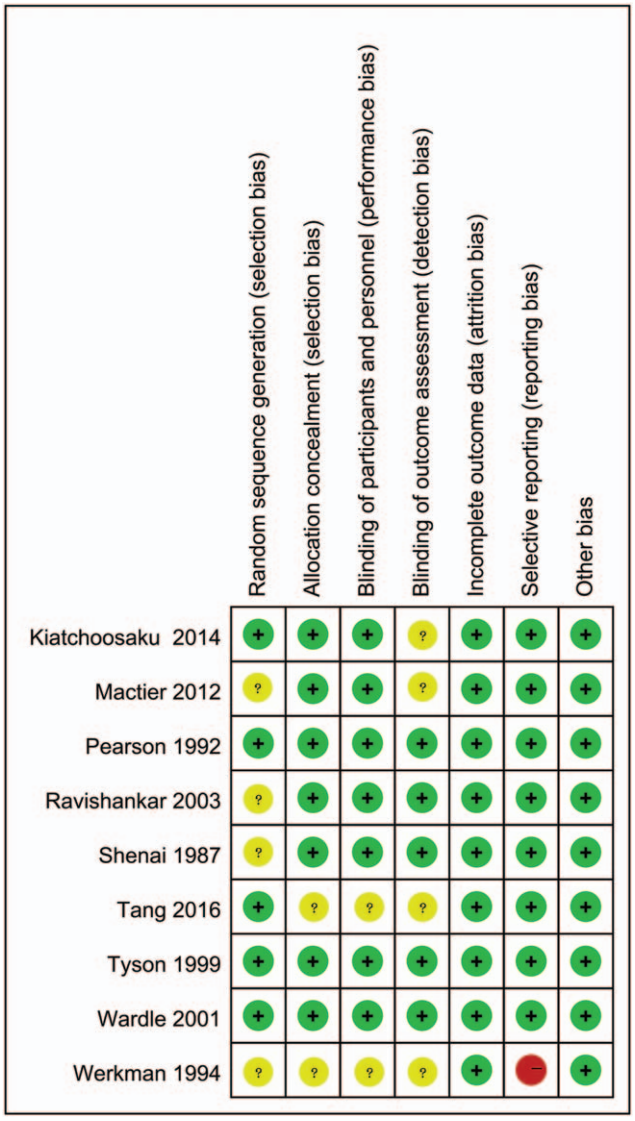

Figure 3. Risk of bias summary.

The mortality Seven RCTs[7,13,15–19] reported the mortality among two groups. No significant heterogeneity was found among included RCTs ($I^2 = 0\%$). The analysis result showed that there was no significant difference in the mortality among two groups (OR = 0.98, 95%CI [0.72–1.34], Fig. 4F).

3.5. Sensitivity analysis

The sensitivity analyses were performed by excluding single RCT one by one. The results of sensitivity analysis of all outcomes had indicated no substantial result changes among the overall estimates.

3.6. Publication bias

The publication bias was evaluated with funnel plot. The funnel plots (Fig. 5) for all synthesized outcomes remained symmetrical, indicating that there was no significant publication bias.

4. Discussion

Vitamin A deficiency is a global public health problem.[21] Vitamin A is mainly transmitted from the mother through the placenta to the fetus in the third trimester. Therefore, the deficiency vitamin A is prevalent in premature infants.[22] Premature birth and low birth weight are important risk factors for BPD.[23] The prevalence of BPD in preterm infants with birth weights of 501 to 750 g, 1000 g, 1250 g, and 1500 g were 42%, 25%, 11%, and 5%, respectively.[24] Another study[25] has reported that 97% preterm infants with birth weight <1250 g have BPD. The Canadian Newborn Collaboration[26] reported that the incidence of BPD among surviving infants with a gestational age of <25 weeks was 28.1%, while the incidence of BPD was only 4% for infants born with a gestational age of 29 to 32 weeks. Previous studies[27,28] have shown that in the neonates with younger gestational age and the lower birth weight, the vitamin A deficiency is more serious. Meanwhile, BPD is also mainly seen in premature infants with low gestational age,[29] suggesting that there may be a relationship between the vitamin A deficiency and BPD. The results of this present meta-analysis have revealed that the vitamin A supplementation can reduce the occurrence of BPD in premature infants, even rough no significant differences on the incidence of ROP, NEC, IVH, sepsis, and mortality were found.

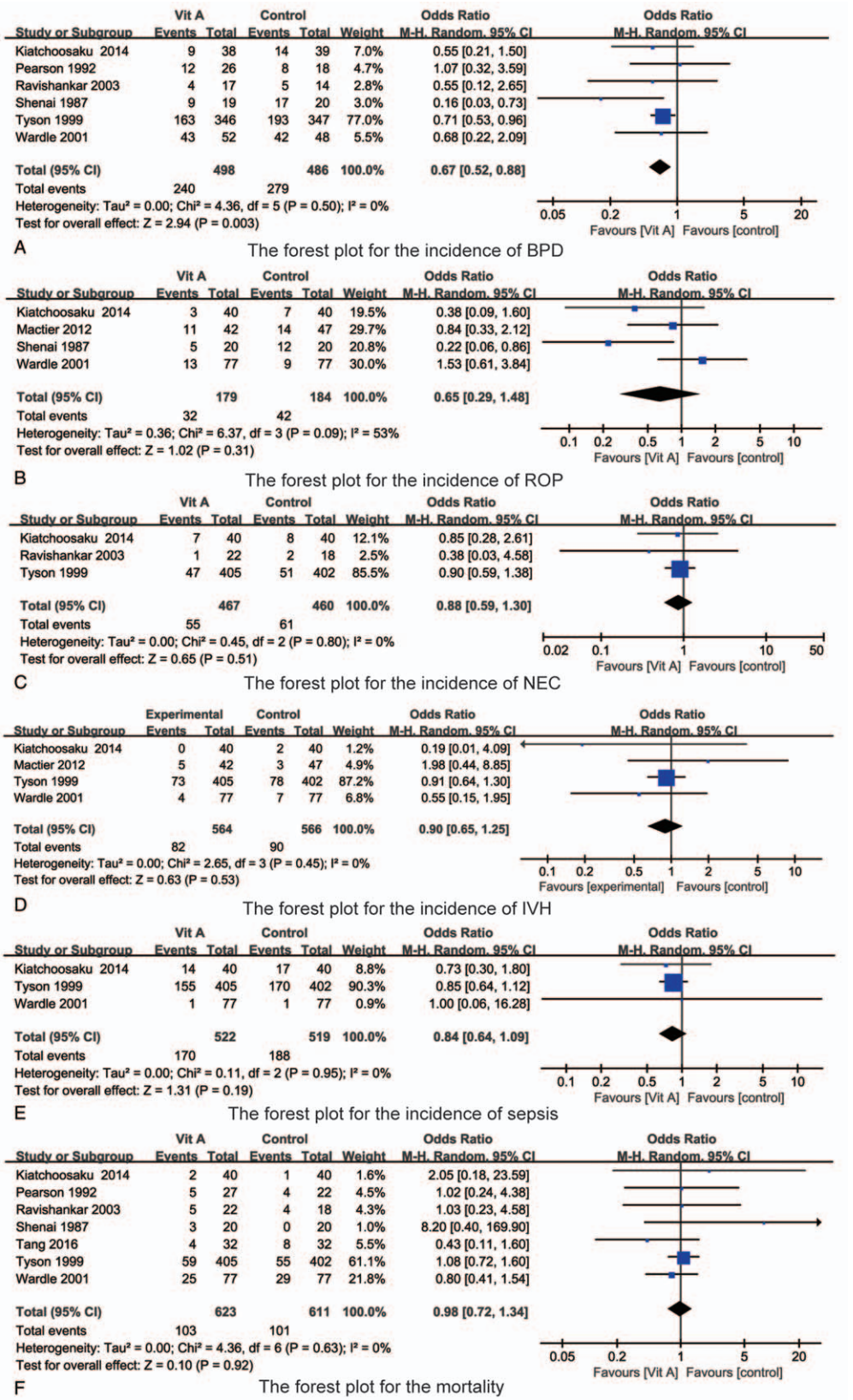

Figure 4. The forest plots for synthesized outcomes.

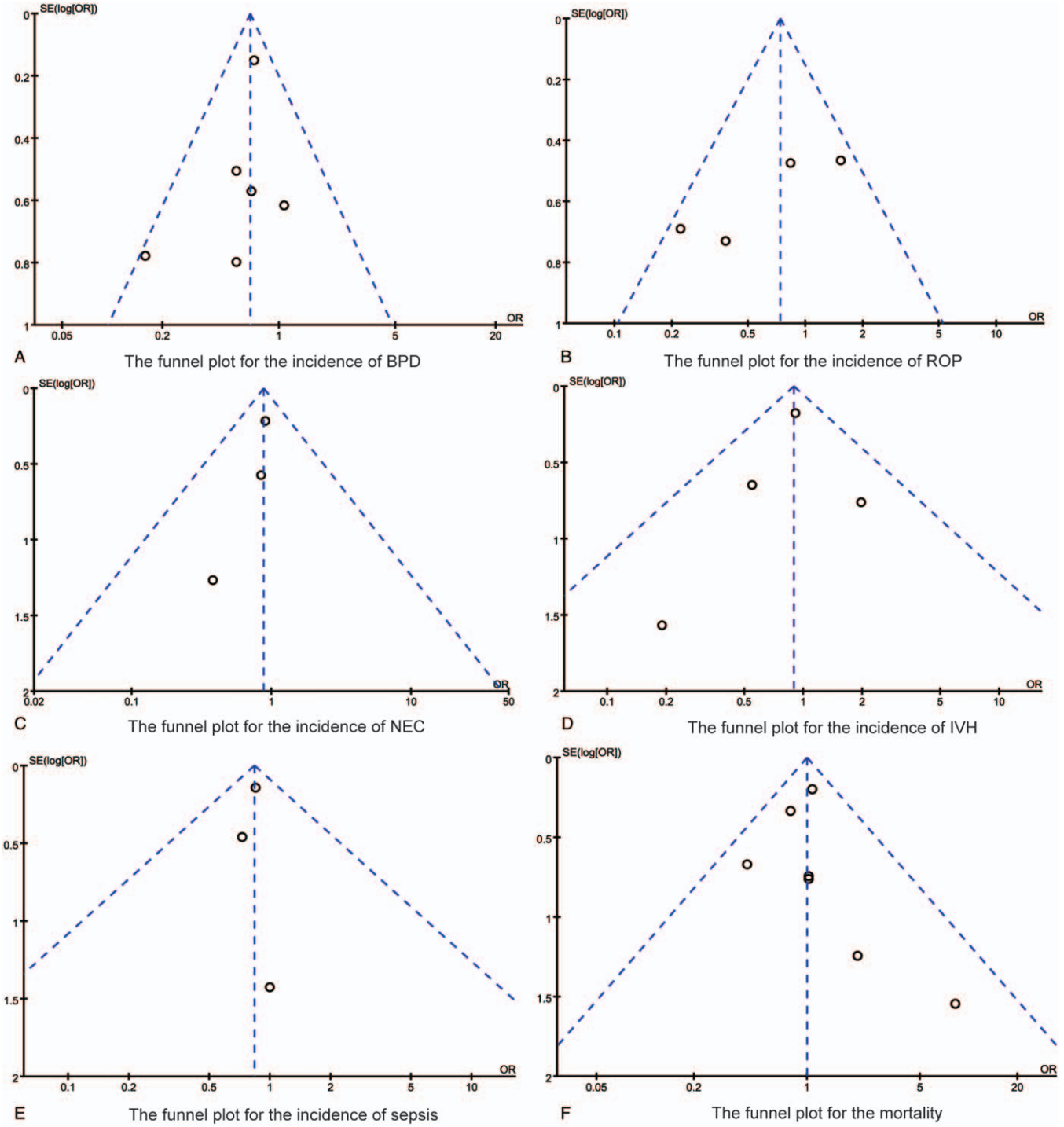

Figure 5. The funnel plots for synthesized outcomes.

Previous studies[30,31] have suggested that vitamin A activates SP-B mRNA transcription through the RA-RAR/RXR pathway and tissue-specific thyroid transcription factor (TTF-1) and other factors, increasing SP-B expression. Several reports[32,33] have shown that the lack of vitamin A can cause the content of SP-A, SP-B, and SP-C mRNAs to decrease, and at the same time reduce the expression of fatty acid synthase (FAS) gene, thus affecting the synthesis of phospholipid precursors. Vitamin A may increase phospholipid and lung surfactant protein synthesis through the above two pathways to promote the lung surfactant synthesis, and thus promotes lung development and maturity.[34] In addition, it may be related to the antioxidant protection of vitamin A and the promotion of repair mechanisms after lung injury.[35]

With the use of clinical vitamin A, reports on its adverse reactions have also emerged. The pain and sepsis are the two most commonly see adverse reaction.[36] Therefore, not only the efficacy of vitamin A, but also its safety in premature infants is

worthy of attention and discussion. Previous studies have shown that vitamin A can reduce the incidence of BPD in preterm infants without serious adverse reactions,[37] but Chabra et al[38] have observed an increase in the incidence of infection and sepsis in children receiving vitamin A. The relevant complications of the two groups of patients in the included nine RCTs are not significantly different. This shows that supplementing vitamin A to prevent BPD in preterm infants may be safe, but further verification is still necessary.

Previous experiments[39,40] in rats have found that vitamin A has a significant effect on lung differentiation and maturation, mainly in the following two aspects. In contrast, lack of vitamin A can cause metaplasia of trachea and bronchial squamous epithelium, and supplementation of vitamin A-related agents can improve its morphological changes.[41] In contrast, vitamin A can affect lung gene expression.[42] Retinyl esters, RBP, and retinoic acid binding proteins can accumulate in the lungs. At the same time, some vitamin A subtypes are expressed in the lungs. The expression of the aforementioned proteins and retinoic acid regulated genes has relevance. If the retinyl ester in the lung is obviously consumed, the cellular RBP level will change significantly, indicating that vitamin A is involved in lung development. Some scholars[43] supplemented the animal model of BPD of premature lambs with vitamin A and have found that it can improve alveolar formation and alveolar capillary growth, reduce the expression of pulmonary parenchymal elastin messenger ribonucleotides and the accumulation of elastic fibers, and achieve better gas exchange. At the same time, some scholars[44] believe that vitamin A deficiency may be one of the reasons for the delayed embryonic lung development in rats by monitoring the levels of related proteins in the rats with absence of fetal lung development. The purpose of this study is to evaluate the effects and safety of BPD by vitamin A. However, the diagnosis can only be made when the oxygen is inhaled 28 days after birth or corrected for gestational age of 36 weeks.[45] Therefore, the focus should also be put on the prevention of BPD.

Several limitations of this present study should be considered. First, the number of high-quality studies on the role of vitamin A in premature infants remains limited, and we failed to conduct subgroup analyses on the results of ROP, future studies with rigorous design are needed. Secondly, the included studies did not observe the long-term neurodevelopment on the painful stimuli caused by repeated intramuscular injections. The longer follow-up periods are needed. Thirdly, the dose of vitamin A in the nine RCTs included in this study varied from 1500 to 10,000 IU, the dose and effect between vitamin A and related outcomes should be further elucidated in the future.

5. Conclusions

In conclusion, vitamin A supplementation is beneficial to reduce BPD in premature infants, and there are no significant differences on the incidence of ROP, NEC, IVH, sepsis, and mortality between two groups. Vitamin A supplementation may be a viable option for the prophylaxis of BPD in premature infants. However, at present, there is still a lack of evidence-based evidence on the administration approaches and dosages of supplementing vitamin A. Limited by the number and quality of included studies, the role of vitamin A in premature infants should be further clarified by more high-quality studies.

Author contributions

Y D designed research; Y D, Z C conducted research; Y D, Y L analyzed data; Y D wrote the first draft of manuscript; Y D had primary responsibility for final content. All authors read and approved the final manuscript.

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Writing – original draft: Yueqin Ding, Zhifeng Chen.
Writing – review & editing: Yueqin Ding.

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