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[Intervention Review]

Vitamin A supplementation for postpartum women

Julicristie M Oliveira[1a], Roman Allert[2,3b], Christine E East[4]

[1]School of Applied Sciences, University of Campinas, São Paulo, Brazil. [2]Cochrane Germany, Medical Center - University of Freiburg, Freiburg, Germany. [3]Department of Obstetrics and Gynaecology, University Hospital Frankfurt, Goethe University, Frankfurt, Germany. [4]School of Nursing and Midwifery/Maternity Services, Monash University/Monash Health, Clayton, Australia

[a]These authors contributed equally to this work. [b]These authors contributed equally to this work

Contact address: Julicristie M Oliveira, School of Applied Sciences, University of Campinas, Rua Pedro Zaccaria, 1300, Limeira, São Paulo, 13484-350, Brazil. julicristie.oliveira@fca.unicamp.br, juli.padma@gmail.com.

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ABSTRACT

Background

In areas where vitamin A deficiency (VAD) is a public health concern, the maternal dietary intake of vitamin A may be not sufficient to meet either the maternal nutritional requirements, or those of the breastfed infant, due the low retinol concentrations in breast milk.

Objectives

To evaluate the effects of vitamin A supplementation for postpartum women on maternal and infant health.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (8 February 2016), LILACS (1982 to December 2015), Web of Science (1945 to December 2015), and the reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) or cluster-randomised trials that assessed the effects of vitamin A supplementation for postpartum women on maternal and infant health (morbidity, mortality and vitamin A nutritional status).

Data collection and analysis

Two review authors independently assessed trials for inclusion, conducted data extraction, assessed risk of bias and checked for accuracy. We assessed the quality of the evidence using the GRADE approach.

Main results

Fourteen trials of mainly low or unclear risk of bias, enrolling 25,758 women and infant pairs were included. The supplementation schemes included high, single or double doses of vitamin A (200,000 to 400,000 internation units (IU)), or 7.8 mg daily beta-carotene compared with placebo, no treatment, other (iron); or higher (400,000 IU) versus lower dose (200,000 IU). In all trials, a considerable proportion of infants were at least partially breastfed until six months.

Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo or no treatment)

Maternal: We did not find evidence that vitamin A supplementation reduced maternal mortality at 12 months (hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.44 to 2.21; 8577 participants; 1 RCT, *moderate-quality evidence*). Effects were less certain at six months (risk ratio (RR) 0.50, 95% CI 0.09 to 2.71; 564 participants; 1 RCT; *low-quality evidence).* The effect on maternal morbidity (diarrhoea, respiratory

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infections, fever) was uncertain because the quality of evidence was *very low* (50 participants, 1 RCT). We found insufficient evidence that vitamin A increases abdominal pain (RR 1.28, 95% CI 0.95 to 1.73; 786 participants; 1 RCT; *low-quality evidence*). We found *low-quality evidence* that vitamin A supplementation increased breast milk retinol concentrations by 0.20 µmol/L at three to three and a half months (mean difference (MD) 0.20 µmol/L, 95% CI 0.08 to 0.31; 837 participants; 6 RCTs).

Infant: We did not find evidence that vitamin A supplementation reduced infant mortality at two to 12 months (RR 1.08, 95% CI 0.77 to 1.52; 6090 participants; 5 RCTs; *low-quality evidence*). Effects on morbidity (gastroenteritis at three months) was uncertain (RR 6.03, 95% CI 0.30 to 121.82; 84 participants; 1 RCT; *very low-quality evidence*). There was *low-quality evidence* for the effect on infant adverse outcomes (bulging fontanelle at 24 to 48 hours) (RR 2.00, 95% CI 0.61 to 6.55; 444 participants; 1 RCT).

Supplement (vitamin A as retinyl) 400,000 IU versus 200,000 IU

Three studies (1312 participants) were included in this comparison. None of the studies assessed maternal mortality, maternal morbidity or infant mortality. Findings from one study showed that there may be little or no difference in infant morbidity between the doses (diarrhoea, respiratory illnesses, and febrile illnesses) (312 participants, data not pooled). No firm conclusion could be drawn on the impact on maternal and infant adverse outcomes (limited data available).The effect on breast milk retinol was also uncertain due to the small amount of information available.

Authors' conclusions

There was no evidence of benefit from different doses of vitamin A supplementation for postpartum women on maternal and infant mortality and morbidity, compared with other doses or placebo. Although maternal breast milk retinol concentrations improved with supplementation, this did not translate to health benefits for either women or infants. Few studies reported on maternal and infant mortality and morbidity. Future studies should include these important outcomes.

PLAIN LANGUAGE SUMMARY

Vitamin A supplementation for postpartum women

What is the issue?

Breastfeeding is expected to provide for the infant's needs in the early months of life. However, if the mother is undernourished herself, the infant may not receive all the nutrients they need. Vitamin A is important for immunity and helping the infant stay healthy, so if the mother does not have enough vitamin A intake in her diet, the infant may also not receive enough in the breast milk.

Why is this important?

In areas where vitamin A deficiency is a public health concern, the maternal dietary intake of vitamin A may be not sufficient to meet either the maternal nutritional requirements, or those of the breastfed infant, due the low concentrations in breast milk. Many studies have been carried out to address this concern in countries where vitamin A deficiency is common.

What evidence did we find?

We reviewed 14 trials. The evidence in general was found was to be of low quality. These studies involved the mothers being given vitamin A or not, within the first six weeks after giving birth, or compared a high dose of vitamin A with a low dose. Our review looked at the overall health of the mothers and their infants, any adverse effects and the levels of retinol, which is a by-product of vitamin A, in the mother's breast milk. There was no change in how many mothers or babies died or were unwell. The mothers and their babies did not experience adverse effects. There was evidence of improved amounts of retinol in breast milk.

What does this mean?

In summary, although extra vitamin A given to the mother may slightly improve the amount of this nutrient in her breast milk, it probably makes little or no difference to deaths in the mother or baby. It may lead to little or no difference in any adverse effects to the mother or baby.

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Summary of findings for the main comparison. Vitamin A supplementation (200,000 to 400,000 IU) compared to placebo or no treatment in postpartum women

Vitamin A supplementation (200,000 to 400,000 IU) compared to placebo or no treatment in postpartum women

Patient or population: Postpartum women
Setting: Low- and middle-income settings (India, Bangladesh, Indonesia, Tanzania, Gambia, Zimbabwe, Kenya, Ghana, Peru and Brazil)
Intervention: Vitamin A supplementation (200,000 to 400,000 IU)
Comparison: Placebo or No treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo or No treatment	Risk with Vitamin A supplementation (200 000 to 400 000 IU)				
Maternal mortality follow-up: 12 months	Study population		HR 1.01 (0.44 to 2.21)	8577 (1 RCT)	⊕⊕⊕⊖ MODERATE [1]	ZVITAMBO Study Group: We calculated HR from Kaplan-Meier-Curve using Cox model. Ayah 2007: Effects on maternal mortality at 6 months were imprecise (0.50, 95% CI 0.09 to 2.71; 6 deaths, N = 564)
	3 per 1000	3 per 1000 (1 to 6)				
Maternal morbidity (diarrhoea, respiratory infections, fever) follow-up: 3 months	Effect is uncertain because the quality of evidence available is very low		-	50 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2 3]	Roy 1997; diarrhoea: 27/2281 days with vitamin A vs 15/2281 with placebo respiratory infections 82/2281 days with vitamin A vs 125/2281 with placebo fever: 30/2281 days with vitamin A vs 28/2281 with placebo; no statistical comparison performed[11]
Maternal adverse effects after administration: abdominal pain follow-up: 1.25 days	Study population		RR 1.28 (0.95 to 1.73)	786 (1 RCT)	⊕⊕⊖⊖ LOW [4]	Subset of participants from the ZVITAMBO Study Group
	162 per 1000	207 per 1000 (153 to 279)				
Maternal breast milk retinol concentration follow-up: mean 3-3.5 months	The mean maternal breast milk retinol concentration ranged from 0.44 to 1.82 mcmol/L	The mean maternal breast milk retinol concentration in the intervention group was 0.2 mcmol/L higher (0.08 higher to 0.31 higher)	-	837 (6 RCTs)	⊕⊕⊖⊖ LOW [5 6]	Ayah 2007; Martins 2010; RETIBETA Project; Roy 1997; Stoltzfus 1993a; Vinutha 2000

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Infant mortality follow-up: range 2 months to 12 months	Study population		RR 1.08 (0.77 to 1.52)	6090 (5 RCTs)	⊕⊕⊖⊖ LOW [7 8]	Ayah 2007; Martins 2010; Newton 2005; Venkatarao 1996; ZVITAMBO Study Group
	20 per 1000	22 per 1000 (16 to 31)				
Infant morbidity (gastroenteritis) follow-up: 3 months	Study population		RR 6.03 (0.30 to 121.82)	84 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2 9]	Vinutha 2000. There were zero events for gastroenteritis in the control group and so it was not possible to calculate anticipated absolute effects.
	see comment	see comment				
Infant adverse effects: bulging fontanelle follow-up: range 1 days to 2 days	Study population		RR 2.00 (0.61 to 6.55)	444 (1 RCT)	⊕⊕⊖⊖ LOW [10]	Ayah 2007
	18 per 1000	36 per 1000 (11 to 118)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **HR:** Hazard ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to serious imprecision (95% CI includes both appreciable benefit and harm)
[2] Downgraded one level due to serious risk of bias (unclear allocation sequence generation and concealment; participants and personnel not blinded)
[3] Downgraded two levels due to very serious imprecision (very small size, N = 50)
[4] Downgraded two levels due to very serious imprecision (95% CI includes both appreciable benefit and harm)
[5] Downgraded one level due to serious risk of bias (allocation sequence generation and concealment unclear in three of six studies)
[6] Downgraded one level due to serious inconsistency (I^2 = 58%)
[7] Not downgraded for risk of bias (sensitivity analysis excluding three trials with unclear allocation randomisation did not change effect estimate)
[8] Downgraded one level due to serious imprecision (95% CI includes both appreciable benefit and harm)
[9] Downgraded two levels due to very serious imprecision (very few events, N = 2; 95% CI includes appreciable benefit and harm)
[10] Downgraded two levels due to very serious imprecision (very few events, N = 12; 95% CI includes both appreciable benefit and harm)
[11]Numerator: number of cumulative days of illness, denominator: number of people-days of follow-up. The number of people-days has been extracted from the original reference.

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BACKGROUND

Description of the condition

Vitamin A functions and sources

Vitamin A is a common term for a set of fat-soluble substances, such retinol, retinal, retinoic acid, retinyl ester, and pro-vitamin A carotenoids (Butte 2002; FNB 2000; Tanumihardjo 2011). It has an essential role in visual and immune systems, maintenance and proliferation of epithelial cells, growth and physical development, reproduction and gene expression (FAO/WHO 2001; FNB 2000; Tanumihardjo 2011; WHO 1998), and during all vital stages of pregnancy and lactation (WHO 1998).

The dietary sources can be divided in pro-vitamin A and pre-formed vitamin A. Some vegetables such as buriti, carrot, papaya, pumpkin, and red palm oil are sources of pro-vitamin A (alfa- and beta-carotene, alfa-cryptoxanthin). Human breast milk, dairy products (whole milk, yogurt, cheese, and milk cream), egg yolk, fish oils and liver are sources of pre-formed vitamin A (FAO/WHO 2001; FNB 2000).

Newborns and infants, in many countries, can only meet their vitamin A requirements through breastfeeding (Butte 2002; WHO 1998), which is associated with maternal nutritional status and food consumption (Butte 2002). Thus, in lactating women with adequate vitamin A status and intake, their breast milk retinol concentrations are sufficient to meet the newborns' and infants' needs until the sixth month of life (Butte 2002). On the other hand, in lactating women with vitamin A deficiency (VAD), their breast milk retinol concentrations can be sub-optimal to meet the newborns' and infants' needs, as well as, to build or preserve hepatic reserves of this micronutrient (Butte 2002; WHO 1998).

According to the World Health Organization (WHO) (WHO 2009a), several risk factors increase the overall burden of disease in low-income countries. The most important of these include infant underweight, low proportion of breastfeeding, and nutrition deficiencies, including iron, vitamin A and zinc, with these factors contributing 20% to the disease burden in these areas, especially of infectious disease.

Vitamin A indicators

Specific indicators of VAD can be considered as biological, histological, functional and biochemical (Tanumihardjo 2004; Tanumihardjo 2011), and also in its clinical and subclinical manifestations (subdivided in degrees: severe, moderate and mild) (WHO 1996). Xerophthalmia, a biological indicator, is a generic term that comprises all ocular clinical signs of VAD, including conjunctival xerosis, Bitot's spots, corneal xerosis, ulceration, keratomalacia, and corneal scars (Wasantwisut 2002; WHO 1996). Conjunctival impression cytology (CIC), a histological indicator, is used to assess the morphological changes in the cells on the surface of the eyes in VAD (Congdon 2002; Tanumihardjo 2011). Night blindness and impaired adaptation to darkness can be considered as functional indicators (Tanumihardjo 2011; WHO 1996).

Serum retinol concentration (cut-off: $\leq$ 0.7 µmol/L), breast milk retinol concentration (cut-off: $\leq$ 1.05 µmol/L or 0.28 µmol/g fat), relative dose response (RDR; cut-off: $\geq$ 20%), and modified relative dose response (MRDR; cut-off: $\geq$ 0.06) are VAD biochemical and subclinical indicators (WHO 1996). Both RDR and MRDR are indirect methods to estimate vitamin A hepatic reserves (Tanumihardjo 2004; Tanumihardjo 2011).

Vitamin A and adverse effects

According to Rasmussen 1998, the evidence regarding the teratogenic effects of high amounts of pre-formed vitamin A in women at the beginning of pregnancy are scarce. Moreover, case-control and prospective investigations failed to establish an association between maternal vitamin A intake with fetal teratogenicity (Azaïs-Braesco 2000). Thus, only case reports have described a link between this adverse outcome and the metabolites, such as trans retinoic acids and 13-cis retinoic acids, until the sixth week of pregnancy (Rasmussen 1998).

Allen and colleague (Allen 2002) have reviewed the maternal and infant secondary adverse effects after high doses of vitamin A supplementation and noted that the possible acute symptoms observed were enhanced cerebrospinal fluid pressure, bulging fontanelle, headache, fever, nausea, vomiting, diarrhoea, blurred vision, drowsiness and impaired muscular co-ordination.

Vitamin A and metabolic interactions

Zinc probably plays an important role in many steps of vitamin A metabolism, such as absorption, transport, mobilisation and utilisation (Christian 1998; Hess 2005).

According to Christian 1998, who reviewed the interaction between these micronutrients, zinc deficiency may for example: impair synthesis of chylomicrons and the uptake by the lymphatic system; reduce the synthesis of retinol-binding protein (RBP) and, consequently, vitamin A circulation and utilisation; impair the oxidation of retinol to retinal, which is crucial for the visual function; and decrease the synthesis of rhodopsin and rod photosensitivity, leading to night blindness and impaired adaptation to darkness.

Although these associations have been observed in laboratory experimental models, cross-sectional and intervention studies in humans are not conclusive concerning the strength of the metabolic interaction between zinc and vitamin A, and its public health implications (Christian 1998; Hess 2005).

In South Africa, a trial conducted in children with HIV and non-HIV, aged six to 24 months, reported no beneficial influence of vitamin A plus zinc supplementation compared to vitamin A or multi-micronutrients on growth. However, in a subgroup analysis, an improvement was noted on reducing the impact of episodes of diarrhoea on non-HIV children growth (Chhagan 2010). In Indonesia, an intervention study carried out with pregnant women reported no positive effect in morbidity, mortality, birth length or weight after vitamin A plus zinc supplementation (Prawirohartono 2013).

It is believed that VAD prejudices iron mobilisation, and utilisation (Hess 2005), but there is disagreement regarding its role in absorption (Garcia-Casal 1998; Hess 2005; Walczyk 2003). Some intervention studies in humans were developed with the aim to assess the effect of vitamin A supplementation on iron and haematological parameters, and most of them have shown a positive impact in pregnant women and schoolchildren regarding anaemia, especially when vitamin A was combined with iron (Michelazzo 2013).

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According to Zimmermann 2006 and Hess 2005, the ways whereby vitamin A may affect iron status also include influences on the erythropoietic process, as well as on immune function, and the consequent reduction of the risk of infection and the associated anaemia.

Regarding absorption, Garcia-Casal 1998 has suggested that vitamin A and iron form a complex, which enhances its uptake, but Walczyk 2003 observed no beneficial effect of this vitamin. Some studies have shown that iron deficiency impairs vitamin A metabolism (Oliveira 2008a), probably through a decrease in hepatic mobilisation and serum retinol concentrations (Jang 2000; Strube 2002). In Mexico, a trial developed with pre-school children pointed out that iron supplementation improved the vitamin A nutritional status (Muñoz 2000).

Vitamin A deficiency (VAD)

The global distribution of VAD, published by the WHO in 1995, classified countries by its importance as a public health problem, based on clinical (ocular manifestations) and subclinical (serum retinol) indicators. The geographical regions with the highest proportions of VAD were Africa, Asia and Latin America (WHO 1995).

The most recent report of VAD was presented by WHO in 2009, and included data from 1995 to 2005. According to this document, Africa and South-East Asia were the more affected regions. Although the studies and surveys included to estimate the magnitude of the problem used different methodologies, it is understood that the prevalence of xerophthalmia among pre-school children decreased, but the subclinical VAD (based on low serum retinol concentration) in pre-school children and pregnant women increased, probably due to improved assessment techniques, and larger population samples (WHO 2009b). The VAD data from lactating women were not considered in this report.

Studies carried out around the world suggested that VAD is still a public health concern in some regions and countries. In South Asia, the prevalence of subclinical VAD in children under six years ranged from 28% to 57% (Akhtar 2013). In India, the proportion was 62% in pre-school children from rural areas (Laxmaiah 2012). In Bangladesh, the prevalence was 18.5% in pregnant women (Lee 2008) and 37% in lactating women (Ahmed 2003). In South Africa, the proportions were 21.4% and 49.3% in postpartum women and their newborns, respectively (van Stuijvenberg 2015).

Regarding Latin American and Caribbean countries, the prevalence of subclinical VAD in children under six years was less than 10% in Central America. However, the proportions were 17.4% and 13.0% in Brazil and Peru, respectively. The prevalence among women was 12.3% in Brazil and 8.7% in Peru (Cediel 2015).

The ranges in prevalence of breastfeeding, maternal and infant mortality in countries with VAD are important in the context of any public health program involving maternal postnatal supplementation with vitamin A that aims to improve infant nutrition, through improved maternal health.

Breastfeeding prevalences

The global prevalence of exclusive breastfeeding during the first six months of life is estimated by WHO 2015a as 36%. The low- and lower-middle-income groups showed the highest proportions, 47% and 33%, respectively.

The prevalences in Asia, Africa, and America vary by the specific country (WHO 2015a). In Nepal, Bangladesh, and Indonesia, 70%, 64%, and 42% of infants were exclusively breastfed until the sixth month of life (WHO 2015a). In India, the prevalence was 46% (WHO 2014). In Tanzania, the proportion was 50%, followed by Ghana (46%), Gambia (34%), Kenya (32%), and Zimbabwe (31%) (WHO 2015a). The prevalence was 72% in Peru (WHO 2015a) and was 40% in Brazil (WHO 2014).

Maternal mortality rates (MMR)

Although there are concerns about the accuracy of maternal mortality estimates, the statistics for 1990 to 2015 presented by WHO 2015b pointed out a 44% overall decrease in the maternal mortality ratio (MMR), from 385 to 216 deaths per 100,000 live births in 1990 and 2015, respectively.

In 2015, almost 99% (302,000) of the total maternal deaths occurred in developing areas. Considering the regions, approximately 66% (201,000) and 22% (66,000) of these deaths occurred in Sub-Saharan Africa and Southern Asia, respectively. The MMR was 546 in Sub-Saharan Africa and there were 176 deaths per 100,000 live births in Southern Asia. Oceania did not account for a great number of deaths (500), but the MMR was one of the highest (187) (WHO 2015b).

Even though developing areas presented the highest MMR, the estimates are not comparable considering different countries within geographical regions. In 2015, the MMR was higher in Nepal (258 deaths per 100,000 live births) than in Bangladesh (176), India (174) or Indonesia (126). The heterogeneity among African countries is also obvious. In Gambia the MMR was 706, followed by Kenya (510), Zimbabwe (443), Tanzania (398) and Ghana (319) (WHO 2015b). This estimate was 13 for both Northern America and Europe (WHO 2015c). In Latin America and Caribbean countries, the rates are still relatively high (60 and 175, respectively). The MMR was 68 in Peru and 44 in Brazil (WHO 2015b).

Infant mortality rates (IMR)

Similarly to maternal mortality, the accuracy of infant mortality estimates is also an important challenge. Even considering this limitation, the statistics for 1990 to 2015 presented by United Nations Children's Fund (UNICEF 2015) described a substantial progress in reducing the infant mortality ratio (IMR) by 50%, from 63 in 1990 to 32 deaths per 1000 live births in 2015.

In 2015, around 98% (4,383,000) of the total infant deaths occurred in developing areas; approximately 46% (2,018,000) and 34% (1,499,000) of these deaths occurred in Sub-Saharan Africa and Southern Asia, respectively. The IMR was 56 in Sub-Saharan Africa and there were 41 deaths per 1000 live births in Southern Asia. Oceania did not account for a considerable number of total deaths (11,000), nevertheless the IMR was one of the highest (40) (UNICEF 2015).

Although developing areas presented the highest IMR, the estimates are not homogenous considering the different countries within geographical regions. In 2015, the IMR was higher in India (38) than in Bangladesh (31), Nepal (29) or Indonesia (23 per 1000 live births). Differences among African countries are also evident. In the Gambia the MMR was 48, followed by Zimbabwe (47), Ghana (43), Kenya (36), and Tanzania (35). This estimate was six and five

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in Northern America and Europe, respectively. In Latin America and Caribbean countries, the rate was 15. The IMR was 15 in Brazil and 13 in Peru (UNICEF 2015).

Description of the intervention

Vitamin A supplements may take a number of forms, for example: as Vitamin A, measured in international units (IU) of retinyl palmitate (3.33 IU or 0.003491 micromol of retinol = 1 microgram or 1 retinol equivalent (RE) (IVACG 2004), in an oil basis or water-miscible formulation, or as beta-carotene, generally in gelatinous capsules.

In 1998 and in 2002, WHO, UNICEF and the International Vitamin A Consultative Group (IVACG) recommended in areas where VAD was a public health concern, high doses of maternal vitamin A supplementation until the sixth week postpartum as an approach to promote women's and infants' health and adequate nutritional status (Ross 2002; WHO 1998). However, the most recent WHO guideline (WHO 2011) that was developed based on systematic reviews (Gogia 2010; Gogia 2011; Oliveira-Menegozzo 2010 (the initial version of this review)), did not reinforce this previous recommendation, and highlighted the role of adequate food consumption in order to promote maternal health and nutritional status.

The WHO 1998 guideline described some scenarios that considered safety and frequency of maternal vitamin A supplementation during the postpartum period in countries where VAD is a public health concern. For non-lactating women, a high dose of vitamin A (over 25,000 IU and usually 200,000 IU) during the first four weeks postpartum could be beneficial. After six weeks, for these women a maximum dose of 10,000 IU daily should be administered. For lactating women, a high dose (200,000 IU) administered until 60 days postpartum could be beneficial for them and, as well as, for their infants through higher breast milk retinol concentrations (WHO 1998). In 2002, WHO (Ross 2002) suggested that two high doses of vitamin A (200,000 IU each), with a minimum of 24 hours apart, could be administered to women until the sixth week postpartum.

The WHO 2011 guideline made recommendations for future research, including the need to evaluate the impact of vitamin A (200,000 IU), exactly at the sixth week postpartum compared to early supplementation for lactating women on breast milk retinol concentrations. Moreover, the metabolic aspects and body distribution (hepatic reserves and secretion through breast milk) after the administration of the high doses were also cited as priorities for further studies.

How the intervention might work

Hypothetically, vitamin A supplementation for postpartum women from populations where VAD is endemic could reduce maternal and infant mortality and morbidity risks. Moreover, the intervention could contribute to building vitamin A hepatic reserves and promote an adequate nutritional status for both mother and infant, thus impacting on morbidity and mortality.

Why it is important to do this review

Considering that VAD remains a public health problem in some countries and regions, intervention studies, public policies and nutrition programs have assessed and recommended vitamin A supplementation during the postpartum period with the aim of improving maternal and infant health. Nevertheless, the countries' and researchers' practices and agendas are not always in agreement with the recommendations of international health agencies, like WHO. Food intake patterns and body composition shifts have occurred globally over the last decades, a phenomenon known as 'nutrition transition', including in regions with a reduction of under-nutrition (Haddad 2015) and of VAD (WHO 2009b). Therefore, changes in a population's overall health status would be expected over time, thus necessitating constant revisions of food and nutrition strategies, and justifying the update of this systematic review of relevant randomised controlled trials regarding maternal vitamin A supplementation during the six weeks of puerperium, that is the postpartum period.

Other reviews have considered vitamin A supplementation in women of childbearing age, during pregnancy and also provided to the newborn/infant (Gogia 2010; Gogia 2011; McCauley 2015). We have therefore focused this review on vitamin A supplementation for postpartum women only. This is an update of the review originally published in 2010 (Oliveira-Menegozzo 2010).

OBJECTIVES

To evaluate the effects of vitamin A supplementation, alone or in combination with other micronutrients (e.g. iron, folic acid, vitamin E) for postpartum women, on maternal and infant health.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials that evaluated the effects of vitamin A supplementation for postpartum women. Cluster-randomised trials were eligible for inclusion but none were identified. Quasi-randomised trials and cross-over studies were not eligible for inclusion.

Types of participants

Studies involving postpartum women, breastfeeding or not, from countries where vitamin A deficiency (VAD) is a concern were eligible. We did not include studies of women with confirmed chronic diseases such as HIV, as we considered these studies to be beyond the scope of this review and have been reviewed elsewhere, for example, Kongnyuy 2009. Maternal data from studies conducted in areas with a high prevalence of HIV without individual diagnostics at baseline were not excluded; only the data of HIV-negative women in studies conducted with both HIV-positive and HIV-negative women were considered.

Types of interventions

Maternal vitamin A supplementation (beta-carotene or retinyl palmitate in oil or water-miscible formulation) alone or in combination with other micronutrients (examples: iron, folic acid, vitamin E) compared with placebo, no intervention, other micronutrient, or a lower dose of vitamin A, commenced at any time during the postpartum period, that is, within 24 hours after birth until the sixth week postpartum were eligible.

Study protocols could include, for example, maternal administration of high doses (given as a single dose of 200,000;

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300,000; or 400,000 IU), or two doses (for a total of 400,000 IU), daily (7.8 mg or 4327 IU) doses, or a combination of higher or lower doses.

Trials that involved continuous daily/weekly supplementation for women during their reproductive years (pre-pregnancy or during pregnancy) were not included, as they have been addressed in another systematic review (McCauley 2015).

In addition to maternal supplementation, some studies also included infant vitamin A supplementation. In these cases, only maternal outcomes were considered for this review, given that outcomes for infant supplementation have been considered in other reviews (Gogia 2010; Gogia 2011). However, infant outcomes were included in our review if they had been measured prior to commencement of infant supplementation.

Types of outcome measures

We reviewed most outcomes for up to 12 months postpartum, with the exception of adverse effects close to the time of vitamin supplementation.

Primary outcomes

Maternal outcomes

1. Mortality.
2. Morbidity (febrile illness, respiratory tract infection, diarrhoea, anaemia and others).
3. Adverse effects of vitamin A within three days after receiving supplement.

Infant outcomes

1. Mortality.
2. Morbidity (febrile illness, respiratory tract infection, diarrhoea, anaemia and others).
3. Adverse effects of vitamin A supplementation within three days after receiving supplement.

Secondary outcomes

Maternal outcomes

1. Serum retinol concentration.
2. Vitamin A hepatic reserves (MRDR or RDR).
3. Breast milk retinol concentration.
4. VAD (clinical: impaired visual adaptation to darkness, night blindness, xerophthalmia; and subclinical: abnormal conjunctival impression cytology (CIC)).

Infant outcomes

1. Serum retinol concentration.
2. Vitamin A hepatic reserves (relative dose response (RDR) or modified relative dose response (MRDR)).
3. Clinical VAD (clinical: signs of xerophthalmia).

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (8 February 2016).

The Register is a database containing over 20,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in *The Cochrane Library* and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Trials Search Co-ordinator searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we searched LILACS - Latin American and Caribbean Health Sciences by Bireme (1982 to December 2015) and Web of Science (1945 to December 2015), using the search strategies detailed in Appendix 1.

For additional searching carried out in previous versions of this review, see: Oliveira 2008b; Oliveira-Menegozzo 2010.

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* Oliveira-Menegozzo 2010.

For this current version, the following methods were used for assessing the 691 studies that were identified as a result of the

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Pregnancy and Childbirth Group register updated search (27) and by the authors additional searches of the LILACS (109) and Web of Science (555) databases.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors (JMO, RA) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author (CEE). We elected to only include studies reported in brief abstracts if they provided sufficient information to allow us to assess risk of bias; if not, such studies would await further assessment pending publication of the full study report.

Data extraction and management

For eligible studies identified in this update, two review authors (JMO, RA) extracted the data using the Pregnancy and Childbirth standard form. We resolved discrepancies or uncertainties through discussion or, if required, we consulted the third review author (CEE). Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we contacted authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (JMO, RA) independently assessed risk of bias for each study included in this update using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement or uncertainty was resolved by discussion or by involving a third assessor (CEE).

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

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- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this update, we assessed the quality of the evidence using the GRADE approach as outlined in the GRADE Handbook in order to estimate the quality of the body of evidence relating to the following outcomes (for the main comparison of vitamin A supplementation versus control (placebo, no treatment, other)):

1. maternal mortality;
2. maternal morbidity;
3. maternal adverse effects of vitamin A supplementation;
4. breast milk retinol concentration;
5. infant mortality;
6. infant adverse effects of vitamin A supplementation;
7. infant morbidity.

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We used the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials if any are identified in future updates of this review. We will adjust their sample sizes using the methods described in the *Handbook* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials are unlikely to be an appropriate design for Pregnancy and Childbirth reviews and were therefore not eligible for inclusion in our review.

Other unit of analysis issues

As trials in Pregnancy and Childbirth may include outcomes for multiple pregnancies, we planned to collect maternal outcome data once for the women and for infant outcomes on the individual babies.

Trials with more than two arms

In the original version of the review (Oliveira-Menegozzo 2010), we did not specify how we would deal with trials that reported three or more groups. As methods have evolved in the intervening period (see Higgins 2011, Section 16.5.4), we retained the process that we had used for the study by Ayah 2007 in the previous version of the review, but have made an adjustment to the numbers of events and total participants in the control group of the RETIBETA Project in this update.

The study by Ayah 2007 involved four groups: two groups of women received vitamin A supplementation and their infants received either vitamin A or placebo. Similarly, two groups of women received the placebo and their infants received either supplemental vitamin A or placebo. The women could only receive either the treatment or placebo, meaning there were effectively only two maternal arms: supplementation or placebo. We therefore reported maternal outcomes from these two groups. As this review did not include infant supplementation within its scope, we only reported infant outcomes if the infant had received the placebo. The women could have received either vitamin A supplementation or placebo. In this way, we avoided any concerns about double-counting.

By contrast, the RETIBETA Project, which involved a total of three groups: two groups each using a different form of vitamin A supplementation (that we reported separately from other studies)

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and a control arm. We halved the numbers of events and participants (rounding up if an uneven number was noted) in the control arm for dichotomous outcomes. For continuous outcomes, we retained the mean and standard deviation and halved the number of participants, consistent with one of the options for dealing with this unit of analysis issue from Higgins 2011 (Section 16.5.4).

We avoided needing to combine data from four arms in the study reported by Newton 2005, as there was sufficient detail available to only include the two postpartum supplementation (or placebo) arms. The other two arms involved supplementation or placebo during pregnancy, which fell outside the scope of this review.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates of this review, if more eligible studies are included, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. Had we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we would not have combined trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses. We considered whether an overall summary was meaningful, and it was, we used random-effects analysis to produce it.

We planned to conduct the following subgroup analyses, if sufficient data were available:

1. type of supplement (vitamin A (retinyl palmitate or water-miscible formulation) or beta-carotene);
2. duration of supplementation (daily, single or double dose);
3. dose of supplement (200,000 to 300,000 IU or 400,000 IU);
4. duration of breastfeeding.

All outcomes were included in the subgroup analysis. It was not possible to conduct subgroup analysis on duration of breastfeeding, but we will include this in future updates, if data become available.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We carried out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor-quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result. We also carried out sensitivity analyses to explore the effect of vitamin A dosage and formulation.

RESULTS

Description of studies

Results of the search

For the updated version of the review, we assessed the eligibility of 691 studies that were identified as a result of the combined searches from the Pregnancy and Childbirth Group's register updated search (n = 27), LILACS (n = 109) and Web of Science (n = 555) databases. After the evaluation, five studies were considered eligible. Two of the studies were included in the review (Fernandes 2012; Martins 2010). Two were added to Studies awaiting classification, because only the trial registry information and abstracts were available, which would not have permitted us to perform a robust data extraction and 'Risk of bias' assessment (Nga 2013; Wang 2012). One was added to Ongoing studies, because only the trial registry and the protocol were available and published (Ahmad 2015). See Figure 1.

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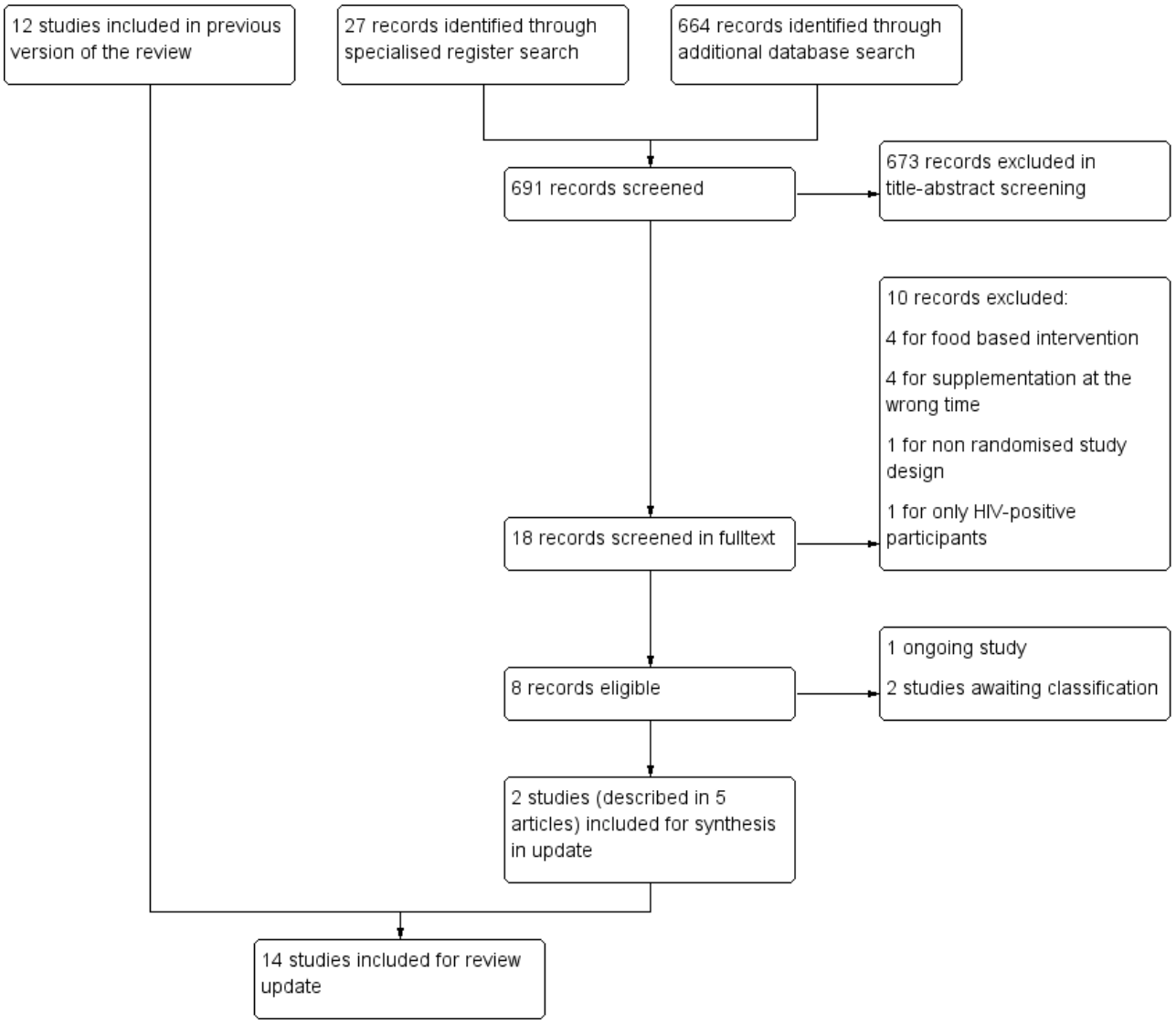
Figure 1. Systematic review flow diagram.



Included studies

We included a total of 14 studies that enrolled 25,758 women and infant pairs residing in low-income settings in India, Bangladesh, Indonesia, Tanzania, Gambia, Zimbabwe, Kenya, Ghana, Peru and Brazil, countries in which women in the studies were likely to have low vitamin A levels and low nutritional status. The Characteristics of included studies table provides further information on these trials. Although all studies reported or implied that postpartum women breastfed their infants, the available details made it impractical to perform subgroup or sensitivity analyses by duration of breastfeeding.

Dosage and duration of vitamin A supplementation

Ten studies (Ayah 2007; Bhaskaram 2000; Martins 2010; Newton 2005; Roy 1997; Stoltzfus 1993a; Venkatarao 1996; Vinutha 2000; WHO/CHD IVASSG; ZVITAMBO Study Group) involved the administration of a single dose of vitamin A in the form of retinyl palmitate or water-miscible formulation (200,000; 300,000 or 400,000 IU) supplementation for women within the first days or weeks postpartum. Nine of the trials compared vitamin A supplementation with placebo (Ayah 2007; Bhaskaram 2000; Martins 2010; Newton 2005; RETIBETA Project; Stoltzfus 1993a; Venkatarao 1996; WHO/CHD IVASSG; ZVITAMBO Study Group). In two studies, women in the control group received no intervention (Vinutha 2000) or were given iron supplementation (as were those in that study's intervention group) (Roy 1997). The RETIBETA Project used a three-group approach of single postpartum dose of vitamin A (as retinyl palmitate) followed by placebo for nine months, placebo at enrolment followed by daily beta-carotene supplementation for nine months, or placebo at enrolment and daily for nine months. Three trials compared a lower dose of vitamin A (200,000 IU) with a higher dose (400,000 IU) (Darboe 2007; Fernandes 2012; Idindili 2007).

The studies reported the dosage in a variety of units: for the purpose of this review, dosages have generally been presented as international units (IU), based on the calculation of 3.33 IU or 0.003491 micromol of retinol = 1 microgram or 1 retinol equivalent (RE) (IVACG 2004).

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Breastfeeding patterns

Ten of the included studies reported that women breastfed their infants, with several studies noting that all or most of the infants were exclusively breastfed (Vinutha 2000 for the duration of the study, Idindili 2007 for the first month, Martins 2010 most until three months), and others indicating that all or most of infants were at least partially breastfed to six months (Bhaskaram 2000; Fernandes 2012; RETIBETA Project; Roy 1997; Venkatarao 1996; WHO/CHD IVASSG; ZVITAMBO Study Group). All four studies that did not specify details of breastfeeding provided strong surrogate evidence to support the likelihood of at least partial breastfeeding. The studies by Ayah 2007 and Darboe 2007 reported breast milk retinol levels at six months postpartum, whilst the study title, background and/or discussion material suggested that the reports from Newton 2005 and Stoltzfus 1993a related to breastfeeding, although the duration or extent cannot be estimated.

Excluded studies

Twenty-six studies were excluded because they used:

1. alternate allocation to intervention or control groups (six studies: Ala-Houhala 1988; Basu 2003; Bezerra 2009; Garcia 2010; Lima 2012; Tchum 2006);
2. supplementation for women during pregnancy (one study: Ahmad 2009), long-term supplementation during reproductive age (three studies: ObaapaVitA; NNIPS-2; West 2011), or after the first six weeks postpartum (four to 12 months postpartum) (three studies: Haskell 2013a; Haskell 2013b; Turner 2013);
3. provision of fat (one study: Alam 2010), of vitamin A rich foods alone (nine studies: Atalhi 2011; Canfield 2001; De Pee 1995; El Hamdouchi 2013; Filteau 1999; Khan 2007; Lietz 2001; Lietz 2006; Ncube 2001), or combined with nutrition counselling (one study: Swaminathan 2015) rather than vitamin A supplements;
4. vitamin A supplementation for women who live with HIV (one study: Humphrey 2006);
5. a study designed to evaluate circulating levels of immune factors following supplementation or placebo, not maternal or infant mortality/morbidity (one study: Gossage 2000). (*See*Characteristics of excluded studies.)

Risk of bias in included studies

We assessed the overall risk of bias in the 14 included trials as being low or unclear (Figure 2; Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

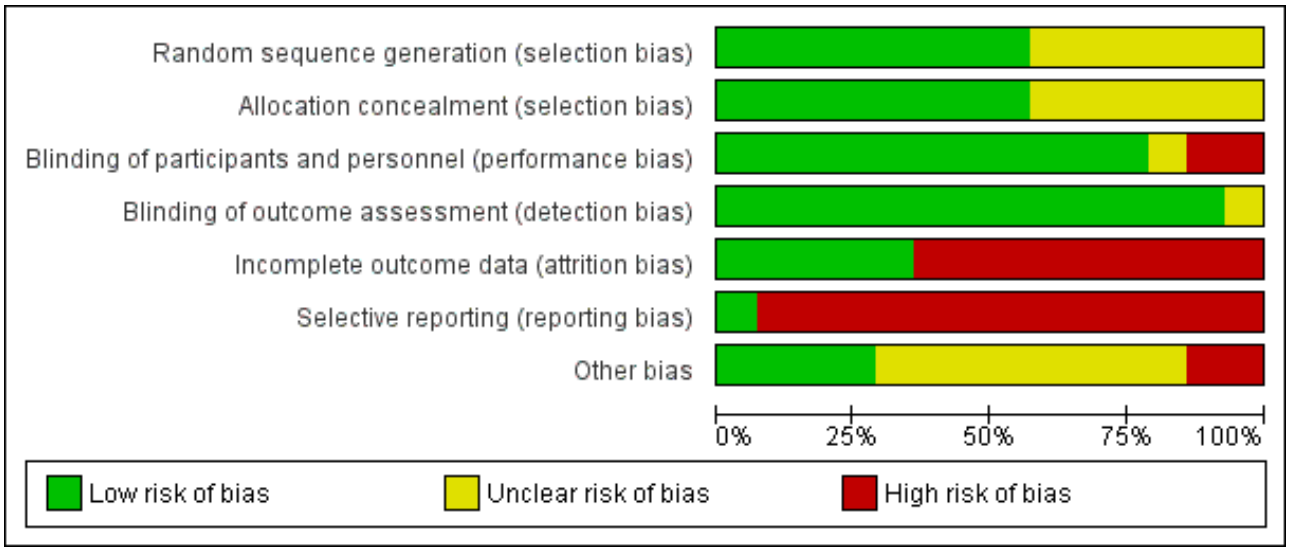

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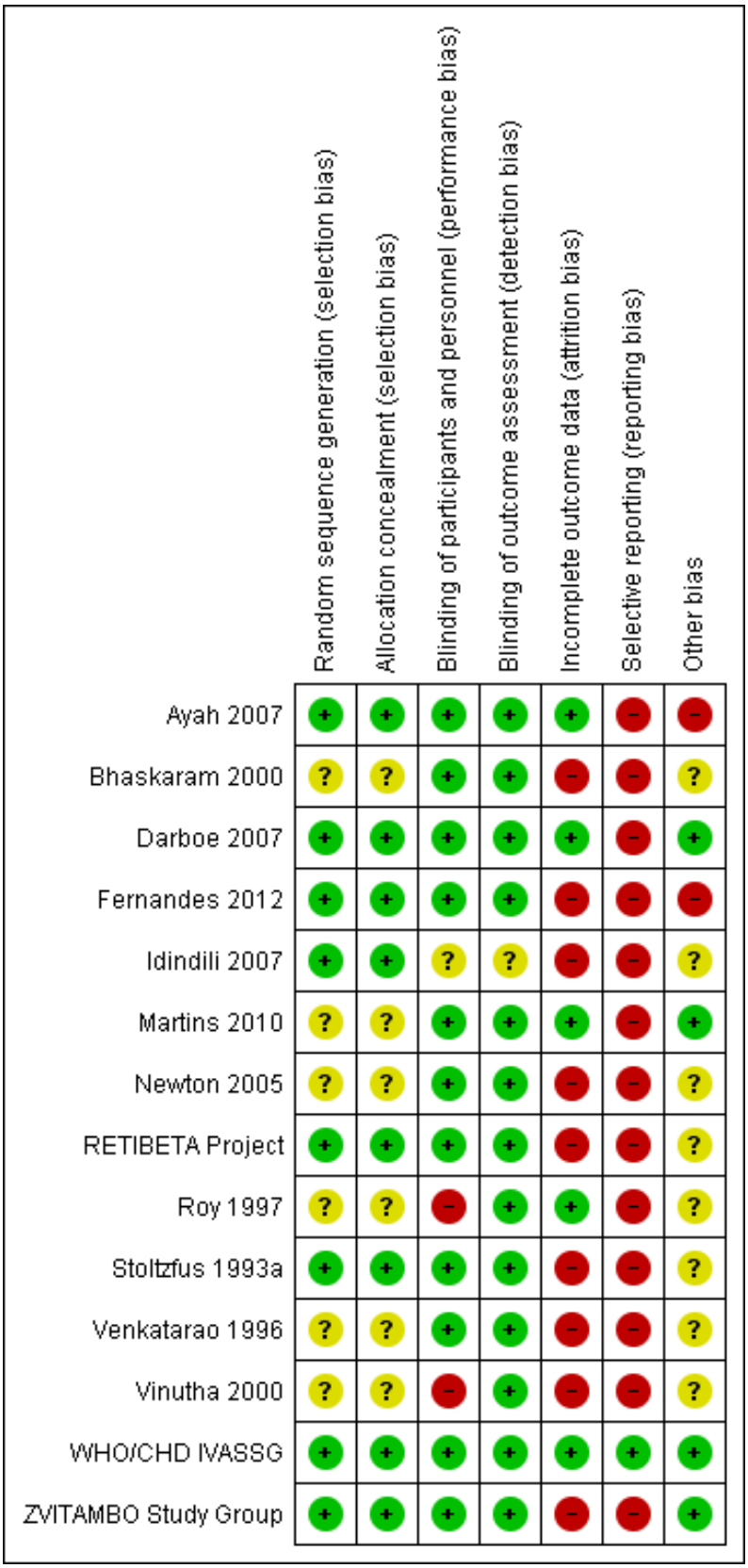
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

We rated eight studies as being of low risk of selection bias (Ayah 2007; Darboe 2007; Fernandes 2012; Idindili 2007; RETIBETA Project; Stoltzfus 1993a; WHO/CHD IVASSG; ZVITAMBO Study Group). In most studies, women and infant pairs were individually randomised in blocks by a computer random number generator and allocation schedules were concealed by being held centrally for the duration of the trial.

The remaining reports from the trials by Bhaskaram 2000, Martins 2010, Newton 2005, Roy 1997, Venkatarao 1996, and Vinutha 2000, provided no information about the method of randomisation and concealment and were therefore rated as being of unclear risk of selection bias.

Blinding

Blinding of participants and personnel (performance bias)

For most studies, the vitamin A and placebo capsules were identical or similar in appearance and/or investigators were not aware of the allocation code (see 'Risk of bias' tables in Characteristics of included studies).

In the study by Idindili 2007, the two different doses of vitamin A were manufactured by the same company, but it was unclear if they were identical in appearance and there was not enough detail to judge whether participants were blinded. In the studies by Roy 1997 and Vinutha 2000, no placebo was used (high risk of bias).

Blinding of outcome assessment (detection bias)

For most studies, allocation codes were kept concealed during the trial duration, field workers were not aware of the aim of the trial or were blinded to the arms, or the outcomes assessed were unlikely to be influenced by blinding (see 'Risk of bias' tables in Characteristics of included studies). In the study by Idindili 2007, there was not enough detail to judge about blinding of outcome assessment.

Incomplete outcome data

In the Venkatarao 1996 trial, there was a 24.2% overall loss of follow-up, distributed similarly between the three groups and attributed to post-randomisation exclusions for medical reasons such as congenital abnormalities or jaundice, migration, and miscellaneous. In the study by Roy 1997, no losses to follow-up were discussed, but data from the tables indicate 100% follow-up. In the Vinutha 2000 clinical trial, the loss of follow-up rate was 22.9%. In the trial by Bhaskaram 2000, the rates of loss to follow-up were 13% and 54% until three and six months postpartum, respectively. Ayah 2007 reported a 12.6% loss to follow-up by three and half months and a 22.9% loss by six and a half months postpartum. In the trial by Darboe 2007, 89.5% of women and infants were followed up until 12 months. Idindili 2007 reported 19%, 20.5%, 22.8% of loss by three, six, and nine months, respectively. Attrition was 11.3% (in both the vitamin A and placebo groups) for HIV-negative women (985/9562) in the report from the ZVITAMBO Study Group. Newton 2005 reported an attrition of 34.6%.

Twenty-three of the total 220 women in the RETIBETA Project missed one or more visits, resulting in follow-up rates of 98%, 95%, and 92% at three, six, and nine months postpartum, respectively, with data reported for these participants in most outcomes. The exception was for maternal hepatic stores of vitamin A and serum retinol concentrations, for which approximately 50% of women were sampled: the report does not specify why all women were not tested. The study by Stoltzfus 1993a had a 9% loss to follow-up in each group by three months and 13% and 5% losses in the vitamin A and control groups respectively by six months - however, the reasons for attrition and exclusions were not reported and ITT analysis was not performed.

Loss of follow-up at nine months for the WHO/CHD IVASSG study was 783 (17%) in the intervention group and 770 (16%) in the placebo group. This increased to 25% and 24.5% in the intervention and control groups respectively by 12 months. Infant death was the only outcome of interest for this review at this time, therefore it was recorded in this review for the nine-month follow-up time, rather than at 12 months. Biochemical markers had been measured in a subgroup of approximately 100 women and their infants from each of the three participating countries: the exact number sampled increased from the first to the second timeframe, which meant we were unable to determine loss to follow-up from the report.

In the trial by Fernandes 2012, different losses of follow-up were reported according to the outcome, however at least 60.45% of women and infant pairs remained until the end of the study. For infant serum and breast milk retinol concentrations, the withdrawals and dropouts were comparable between arms. Regarding maternal serum retinol concentration and infant illness, the withdrawals and dropout differences between the arms were almost 10%.

The losses to follow-up were similar in the intervention and control group in the Martins 2010 study. A high rate of follow-up (89.39%) until three months postpartum was observed.

Selective reporting

We judged all but one trial to be at high risk of selective reporting (WHO/CHD IVASSG) as they did not provide detail on clinical outcomes that would be considered fundamental to a study design; for example, only five of the 14 trials reported infant mortality and only two reported maternal mortality.

Other potential sources of bias

We judged most trials as unclear for risk of other bias, mostly due to a lack of clarity about any influence of funding bodies or not having published protocols.

Effects of interventions

See: **Summary of findings for the main comparison** Vitamin A supplementation (200,000 to 400,000 IU) compared to placebo or no treatment in postpartum women

Comparison 1: Supplement (vitamin A as retinyl, water-miscible or beta-carotene) versus control (placebo, no treatment)

Primary maternal outcomes

Maternal mortality

Two randomised controlled trials (RCTs) evaluated maternal mortality for a total of 9141 women (Ayah 2007; ZVITAMBO Study Group). The study by Ayah 2007 reported no difference in maternal mortality to six months (risk ratio (RR) 0.50, 95% confidence interval

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(CI) 0.09 to 2.71; 564 participants, *low-quality evidence*), Analysis 1.1. There were no reported differences in maternal mortality after vitamin A supplementation or placebo in HIV-negative women followed to 12 months (hazard ratio (HR) 1.01, 95% CI 0.44 to 2.21; 8577 participants; 1 RCT, *moderate-quality evidence*) in the ZVITAMBO Study Group. The adjusted HR and CI were estimated based on the Kaplan-Meier curve reported in the study using Cox model.

Maternal morbidity

One small study of 50 women (Roy 1997) reported no differences in cumulative episodes of fever, respiratory tract infection or diarrhoea (*very low-quality evidence*, see Analysis 1.2; Analysis 1.3; Analysis 1.4).

Adverse effects of vitamin A supplementation

In a subset of 786 women from the ZVITAMBO Study Group, there was no evidence of differences in adverse effects within 30 hours of supplementation, including abdominal pain (RR 1.28, 95% CI 0.95 to 1.73; 786 participants; 1 RCT; *low-quality evidence*), vomiting, headache, blurred vision, drowsiness, nausea or poor appetite following a single dose of 400,000 IU vitamin A or placebo, Analysis 1.5.

Secondary maternal outcomes

Maternal serum retinol

Five studies reported maternal serum retinol values, measured between three and nine months postpartum. In some studies, women were evaluated at three to three and a half (Ayah 2007; Martins 2010; RETIBETA Project; Roy 1997; Stoltzfus 1993a), six to six and a half (RETIBETA Project; Roy 1997; Stoltzfus 1993a), and nine months postpartum (RETIBETA Project; Roy 1997), as described in the following analysis: Analysis 1.6; Analysis 1.7; Analysis 1.8, respectively.

Maternal serum retinol concentrations were enhanced by doses of between 200,000 to 400,000 IU when measured at three to three and half months (mean difference (MD) 0.11 µmol/L, 95% CI 0.03 to 0.19; 704 participants; 5 RCTs), but were not enhanced by the largest single dose (400,000 IU) (MD 0.04 µmol/L, 95% CI -0.01 to 0.09; 402 participants; 1 RCT), or by the daily postpartum administration of 7.8 mg beta-carotene dose (MD 0.10 µmol/L, 95% CI -0.14 to 0.34; 54 participants; 1 RCT), Analysis 1.6. In the subgroup analysis regarding doses of 200,000 to 300,000 IU, a significant increase was also observed (MD 0.17 µmol/L, 95% CI 0.07 to 0.26; 302 participants; 4 RCTs). There was no evidence of a subgroup difference by dose as indicated by the subgroup interaction test (test for subgroup differences: Chi^2 = 6.41, df = 3 (P = 0.09), I^2 = 53.2%).

Maternal serum retinol concentrations were not enhanced by doses of between 200,000 to 400,000 IU, a single dose (400,000 IU), or by beta-carotene at a 7.8 mg daily dose when measured at six to six and half months (MD 0.06, 95% CI -0.06 to 0.18; 533 participants; 4 RCTs; MD -0.02, 95% CI -0.08 to 0.04; 291 participants; 1 RCT; MD 0.05, 95% CI -0.28 to 0.38; 50 participants; 1 RCT; respectively), but were enhanced by doses between 200,000 to 300,000 (MD 0.13, 95% CI 0.03 to 0.23; 242 participants; 3 RCTs), Analysis 1.7. There was no evidence of a subgroup difference by dose as indicated by the subgroup interaction test (test for subgroup differences: Chi^2 = 6.67, df = 3 (P = 0.08), I^2 = 55.0%).

Maternal serum retinol concentrations were not enhanced at nine months by doses of between 200,000 to 300,000 IU or by beta-carotene at a 7.8 mg daily dose (MD 0.00, 95% CI -0.16 to 0.17; 98 participants; 2 RCTs; MD 0.19, 95% CI -0.08 to 0.46; 51 participants; 1 RCT), Analysis 1.8. There was no evidence of a subgroup difference by dose as indicated by the subgroup interaction test (test for subgroup differences: Chi^2 = 1.34, df = 1 (P = 0.25), I^2 = 25.6%).

Vitamin A hepatic reserves

Two studies analysed vitamin A hepatic reserves (reported as relative dose response (RDR) greater than 20% or modified relative dose response (MRDR) ≥ 0.06) at three, six, and nine months postpartum (Analysis 1.9; Analysis 1.10; Analysis 1.11). No improvement in the proportion of women with low hepatic reserves at three months, (RR 0.58, 95% CI 0.16 to 2.08; 191 participants; 2 RCTs; I^2 = 73%), Analysis 1.9, following a single 200,000 to 300,000 IU dose of vitamin A, compared with placebo, neither at six or nine months postpartum. As the data from studies that administrated different doses of vitamin A were pooled, we used a random-effects model because it is not possible to assume that the results would be similar among the trials.

No differences were reported in the RETIBETA Project for this outcome within nine months of daily beta-carotene supplementation and placebo at any times, for example, when measured at nine months (RR 0.59, 95% CI 0.27 to 1.30; 51 participants), Analysis 1.11.

Breast milk retinol

Breast milk retinol concentrations were reported in several formats (retinol concentration, proportion of breast milk retinol < 1.05 µmol/L or < 0.28 µmol/g of fat) in seven studies (Analysis 1.12 to Analysis 1.20). There was*low-quality evidence* that vitamin A supplementation (200,000 to 400,000 IU) was associated with an increased breast milk retinol concentration at three to three and a half months (MD 0.20 µmol/L, 95% CI 0.08 to 0.31; 837 participants; 6 RCTs). This association was also observed in the subgroup analysis with the lower doses (200,000 to 300,000 IU) (MD 0.25 µmol/L, 95% CI 0.12 to 0.37; 415 participants; 5 RCTs; *low-quality evidence*), Analysis 1.12 (test for subgroup differences: Chi^2 = 9.16, df = 3 (P = 0.03), I^2 = 67.2%), but this improvement was not sustained by six to six and a half months postpartum. The subgroup heterogeneity observed in the Analysis 1.12 could be explained by the different effects in the breast milk retinol concentrations. After sensitive analysis, it was possible to observe that the sources of heterogeneity were the Ayah 2007 and Stoltzfus 1993a trials. Both of them used the higher doses, 400,000 IU and 300,000 IU, respectively, but the MD breast milk retinol concentrations between intervention and control group after supplementation vary substantially: 0.08 µmol/L for Ayah 2007 and 0.63 µmol/L for Stoltzfus 1993a. Moreover, the MD for the remaining studies were more homogeneous and varied by 0.17 to 0.37 µmol/L. Thus, the random-effects model was applied.

Subgroup heterogeneity was also found in the following analysis: 1.13.1, 1.13.2, 1.14.1, 1.15.1, 1.16.1 and 1.17.1. As the data from studies that administered different doses of vitamin A were pooled, we used a random-effects model because it is not possible to assume that the results would be similar among the trials.

Daily doses of beta-carotene to nine months postpartum did not improve breast milk retinol at three or six months, but

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did demonstrate improvement for this outcome by nine months postpartum (MD 0.21 µmol/L, 95% CI 0.01 to 0.41, 103 participants; test for subgroup differences: $Chi^2 = 0.11$, df = 1 (P = 0.74), $I^2 = 0\%$), Analysis 1.14, in the RETIBETA Project, compared with placebo.

Supplementation with a single dose of vitamin A (200,000 to 300,000 IU) reduced the proportion of women with low retinol concentration (< 1.05 µmol/L) in breast milk at three months (average RR 0.56, 95% CI 0.37 to 0.84; 304 participants; 3 RCTs; heterogeneity - $Tau^2 = 0.07$, $I^2 = 55\%$; test for subgroup differences: $Chi^2 = 4.88$, df = 1 (P = 0.03), $I^2 = 79.5\%$), Analysis 1.15, but not at six months after delivery (RR 0.65; 95% CI 0.22 to 1.94; 241 participants; 2 RCTs; test for subgroup differences: $Chi^2 = 0.20$, df = 1 (P = 0.66), $I^2 = 0\%$), Analysis 1.16, compared with placebo.

Two studies (RETIBETA Project; WHO/CHD IVASSG) reported the proportion of women with low breast milk retinol levels (< 0.28 µmol/g of fat). Supplementation with a single dose of vitamin A (200,000 IU) or daily beta-carotene 7.8 mg daily for nine months did not improve this measure at three, six, and nine months postpartum (Analysis 1.18; Analysis 1.19; Analysis 1.20).

Although no improvements were noted at three and six months following daily administration of beta-carotene, an improvement was noted by nine months (RR 0.76, 95% CI 0.60 to 0.97; 102 participants; test for subgroup differences: $Chi^2 = 0.79$, df = 1 (P = 0.37), $I^2 = 0\%$) in the RETIBETA Project, Analysis 1.20.

Clinical and subclinical vitamin A deficiency (VAD)

One study, Stoltzfus 1993a, measured abnormal conjunctival impression cytology (CIC) in one or both eyes as the criterion for VAD. There was no difference in the proportion of women with abnormal CIC at three or six months postpartum, following supplementation with vitamin A or placebo (RR 1.00, 95% CI 0.55 to 1.80; 148 participants; RR 0.56, 95% CI 0.27 to 1.17; 142 participants), Analysis 1.21; Analysis 1.22.

Primary infant outcomes

Infant mortality

Infant mortality was assessed at different times in each of the five trials that examined this outcome, ranging from up to two months to up to 12 months (Ayah 2007; Newton 2005; Venkatarao 1996; ZVITAMBO Study Group, Martins 2010), with no differences for vitamin A compared with placebo (RR 1.08, 95% CI 0.77 to 1.52; 6090 participants; 5 RCTs; *low-quality evidence*) (Analysis 1.23). The measure of overall effect did not change meaningfully when we conducted the planned sensitivity analysis of excluding the findings from Newton 2005 and Venkatarao 1996, where there was uncertainty around risk of selection bias and high risk for attrition bias.

Infant morbidity

Three studies (Roy 1997; Venkatarao 1996; Vinutha 2000) evaluated and reported infant morbidity (Analysis 1.24 to Analysis 1.30) *very low-quality evidence*. Although the methods of the Martins 2010 study indicated that infant morbidity was evaluated, the authors did not report this outcome.

Diarrhoea

None of the three studies that considered diarrhoea or gastroenteritis reported any significant differences between the vitamin A supplementation or control groups (Roy 1997 (diarrhoea episodes, 50 participants, P = 0.59), Venkatarao 1996, (RR 1.02, 95% CI 0.98 to 1.06; 456 participants), Analysis 1.24, and Vinutha 2000 (RR 6.03, 95% CI 0.03 to 121.82; 84 participants; *very low-quality evidence*), Analysis 1.26.

Respiratory illnesses

The reduced mean duration of acute respiratory tract infection (3.1 versus 3.7, 50 participants, P < 0.03) in the treatment group reported by Roy 1997 was not noted in the larger study by Venkatarao 1996, which reported no evidence of a difference in overall incidence of one or more episodes to 12 months of age of acute respiratory infection (RR 1.00, 95% CI 0.96 to 1.03; 456 participants), Analysis 1.27, between the supplemented and placebo groups. There was also no evidence of a difference in infant upper respiratory infection to three months (RR 0.91, 95% CI 0.22 to 3.81; 84 participants), Analysis 1.28.

Febrile illness

One small study (Roy 1997) reported a lower mean number of febrile illness episodes (0.1 versus 0.3, 50 participants, P < 0.002) in the vitamin A group compared to the control group, Analysis 1.30.

Adverse effects of vitamin A supplementation

No differences were detected in the potential for developing the adverse effect of bulging fontanelle following vitamin A supplementation (400,000 IU) (RR 2.00, 95% CI 0.61 to 6.55; 444 participants; 1 RCT; *low-quality evidence*) Analysis 1.31.

Secondary infant outcomes

Infant serum retinol

Four studies reported infant serum retinol between three to three and a half, and six to six and a half months. There was no beneficial effect observed in two of the dosing regimens (200,000 to 400,000 IU, or 200,000 IU) used at three to three and half months (MD 0.11 µmol/L, 95% CI -0.05 to 0.26; 379 participants; 4 RCTs; $Tau^2 = 0.02$, $I^2 = 87\%$; MD 0.20 µmol/L, 95% CI 0.00 to 0.39; 215 participants; 3 RCTs; $Tau^2 = 0.01$, $I^2 = 47\%$), Analysis 1.32, and there was evidence of substantial heterogeneity. Similarly, no beneficial effect was observed with the use of 400,000 IU dose versus placebo at three to three and half months, (MD of 0.02 µmol/L, 95% CI -0.03 to 0.07, 164 participants) (Ayah 2007). There were no differences at six to six and a half months in any of the four studies that reported this outcome (Analysis 1.33), for example, the subgroup analysis of 200,000 to 300,000 IU versus placebo yielded a MD 0.03 µmol/L (95% CI -0.02 to 0.09; 289 participants; 3 RCTs), although again there was evidence of substantial heterogeneity. After sensitive analysis, it was observed that the source of heterogeneity was the Vinutha 2000 study that used a water-miscible vitamin A formulation, which probably explains the highest enhancement in serum concentration (MD 0.29 µmol/L) compared to the others studies (MD varying from 0.02 to 0.05 µmol/L).

There was no evidence of a subgroup difference by dose as indicated by the subgroup interaction test.

Vitamin A hepatic reserves

Three studies reported low hepatic vitamin A reserves (Analysis 1.34), but vitamin A hepatic reserves analysed at six to six and half months of infancy were not enhanced by any vitamin A dosing

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regimens, compared with placebo. Substantial heterogeneity was found in these analyses. As the data from studies that administrated different doses of vitamin A were pooled, we used a random-effects model because its not possible to assume that the results would be similar among the trials.

There was no evidence of a subgroup difference by dose as indicated by the subgroup interaction test.

Clinical vitamin A deficiency (VAD)

No study addressed infant clinical VAD.

Comparison 2: Supplement (vitamin A as retinyl) 400,000 IU versus 200,000 IU

Primary maternal outcomes

Maternal mortality

No study addressed maternal mortality.

Maternal morbidity

No study addressed maternal morbidity.

Adverse effects of vitamin A supplementation

Fernandes 2012 noted that the women did not report any adverse effects related to the double (400,000 IU) or single (200,000 IU) doses of vitamin A supplementation, however, no data about this were presented in the publication.

Secondary maternal outcomes

Maternal serum retinol

Two studies presented maternal serum retinol values, assessed between two and six months postpartum, as described in the Analysis 2.1. There was no evidence that a higher dose of maternal vitamin A supplementation (400,000 IU) made any difference to serum retinol concentrations at two months (MD 0.04 µmol/L, 95% CI -0.06 to 0.14; 429 participants; 2 RCTs; test for subgroup differences: $Chi^2 = 3.37$, df = 2 (P = 0.19), $I^2 = 40.7\%$) compared to the standard dose (200,000 IU). The means were not different at four, and six months postpartum (1 RCT, Fernandes 2012).

Vitamin A hepatic reserves

No study addressed maternal vitamin A hepatic reserves.

Breast milk retinol concentration

Breast milk retinol concentrations were reported by three studies, but it was only possible to pool the data from two of them (Analysis 2.2). A double dose of vitamin A supplementation (400,000 IU) was not associated with an increased breast milk retinol concentration at two months (MD -0.01 µmol/L, 95% CI -0.14 to 0.11; 377 participants; 2 RCTs), and at four months (MD -0.03 µmol/L, 95% CI -0.13 to 0.08; 348 participants; 2 RCTs) postpartum, (test for subgroup differences: $Chi^2 = 1.07$, df = 3 (P = 0.78), $I^2 = 0\%$). No difference in breast milk retinol concentration was observed in the trial by Idindili 2007 (780 women randomised) at six months (higher dose: mean = 1.82 µmol/L (standard deviation (SD) = 1.09); lower dose: mean = 1.88 µmol/L (SD = 1.09); P = 0.49) or at nine months postpartum (higher dose: mean = 1.86 µmol/L (SD = 1.19); lower dose: mean = 1.95 µmol/L (SD = 0.97); P = 0.33).

Regarding the proportion of women with low breast milk retinol concentrations, only Darboe 2007 assessed this outcome, and no significant effect was observed (Analysis 2.3).

Clinical and subclinical vitamin A deficiency (VAD)

No study addressed maternal clinical and subclinical VAD outcomes.

Primary infant outcomes

Infant mortality

No study addressed infant mortality.

Infant morbidity

Only one study (Fernandes 2012) assessed the impact of the maternal double dose of vitamin A supplementation on infant morbidity. The rates and RR and CIs were reported for the following infant morbidities (diarrhoea, respiratory illnesses, febrile illness), but the data were not presented in a way that could be used for pooled analysis.

Diarrhoea

No differences were observed for diarrhoea episode rates per 100 children per month (400,000 IU: number of episodes = 98, rate = 13.8; 200,000 IU: number of episodes = 89, rate = 13.3; RR 0.96, 95% CI 0.72 to 1.28, P = 0.80) during the six months postpartum.

Respiratory illnesses

The effects of the double dose was evaluated on acute respiratory infection in episode rates per 100 children per month (Fernandes 2012) until six months postpartum, however no differences were described (400,000 IU: number of episodes = 319, rate = 44.8; 200,000 IU: number of episodes = 310, rate = 46.2; RR 1.03, 95% CI 0.88 to 1.21, P = 0.70).

Febrile illness

For fever episode rates per 100 children per month, no beneficial impact was noted with the maternal double or single doses of vitamin A supplementation (400,000 IU: number of episodes = 185, rate = 26.0; 200,000 IU: number of episodes = 161, rate = 24.0; RR 0.92, 95% CI 0.75 to 1.14, P = 0.46) (Fernandes 2012) during the six months postpartum.

Adverse effects of vitamin A supplementation

In the trial by Darboe 2007, the field workers questioned the women about infant adverse effects (fever, nausea, and bulging fontanelle) at one day before supplementation and on the following three days after supplementation, but no reactions were noted. Fernandes 2012 did not report any infant adverse effects after the double (400,000 IU) or single (200,000 IU) doses.

Secondary infant outcomes

Infant serum retinol

Two studies, Darboe 2007 and Fernandes 2012 (Analysis 2.4), assessed the effects of maternal double (400,000 IU) or single (200,000 IU) doses of vitamin A supplementation on infant serum retinol concentrations at two months postpartum; no significant difference between the regimens was noted (MD 0.01 µmol/L, 95% CI -0.05 to 0.07; 362 participants; 2 RCTs; test for subgroup differences: $Chi^2 = 0.70$, df = 2 (P = 0.71), $I^2 = 0\%$). For the

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following endpoints, four and six months, the absence of effects was maintained.

Vitamin A hepatic reserve

No study addressed infant vitamin A hepatic reserves.

Clinical vitamin A deficiency (VAD)

No signs of xerophthalmia were observed in the trial by Fernandes 2012.

There was no evidence of a subgroup difference by dose as indicated by the subgroup interaction tests for any of the comparisons (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4). Fixed-effect models were used in these analysis.

DISCUSSION

There was no evidence that different doses of vitamin A supplementation for postpartum women could improve maternal and infant mortality and morbidity, compared with other doses, no treatment or placebo. Although maternal serum and breast milk retinol concentrations improved with supplementation, this did not translate to health benefits for either women or infants.

The possible explanations for the absence of a definitive finding are as follows: the limited power of some study samples to detect an effect on mortality and morbidity; the differing maternal mortality rate (MMR) and infant mortality ratio (IMR) at different time points when each trial was developed; the overall positive shift in the MMR and IMR over the decades; the absence of vitamin A deficiency (VAD) or different degrees of severity amongst countries, affected by long-term under nutrition that a single or short course of vitamin A supplementation was unable to redress, as well as, the overall positive shift over the years; the heterogeneity of vitamin A regimens assessed amongst trials; the coexistence of other micronutrient deficiencies, and their interactions; low-quality control of vitamin A content capsules; and the limitations of the biochemical indicators.

Summary of main results

Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other)

Primary maternal outcomes

Maternal mortality was not influenced by single high-dose vitamin A supplementation (400,000 IU) in two studies, Ayah 2007 and ZVITAMBO Study Group, conducted between 1999 to 2001, and 1997 to 2001, respectively, in areas of high MMR. In contrast to our findings, one large study carried out in Nepal, between 1994 and 1997, that evaluated weekly long-term low-dose supplementation with vitamin A or beta carotene (23,300 IU) for women during pregnancy and the postpartum period demonstrated a protective effect of vitamin A for maternal mortality (NNIPS-2). However, other subsequent large studies that assessed similar vitamin A supplementation doses in Bangladesh (JivitA-1 Trial), carried out between 2001 to 2007, and Ghana (ObaapaVitA), between 2000 to 2008, have not been able to replicate this effect.

In the trial by Ayah 2007, 564 women were enrolled, compared with the larger sample in the ZVITAMBO Study Group, for which 14,110 women were randomised, but only data regarding 8577 HIV-negative women with vital status were known, and were included in the present systematic review. Even so, these sample sizes are considerably smaller when compared with the 207,781 women of reproductive age enrolled in the ObaapaVitA study. In this trial, the authors estimated that 82,000 pregnancies would be necessary to detect a 33% reduction in the associated mortality in the intervention arm. However, as the investigators noted, not even in this large sample size study could vitamin A prevent maternal mortality. The differences in MRR by the time each trial was conducted could also have influenced the various study's potential for effect. For example, in Zimbabwe, the MRR was 590 deaths/100,000 live births in 2000, lower than the rate observed in Nepal in 1995 (660) (WHO 2016). Moreover, the overall shifts in MMR over the years (WHO 2015b; WHO 2015c) could limited the impact.

Several **maternal morbidities** are more prevalent in populations known to be vitamin A deficient than in industrialised countries. However, we did not observe a reduction in maternal morbidity after postnatal supplementation. Only a protective effect of vitamin A (300,000 IU) supplementation was observed for the prevalence of abnormal conjunctival impression cytology (CIC) from baseline to six months. This measure of VAD is useful when there is limited access to laboratory assessment of vitamin A status, but not an ideal stand-alone indicator of this micronutrient deficiency (Stoltzfus 1993c). Although the countries in which the studies were conducted would be considered to be areas of VAD, the reduction of its severity over a number of years could explain the present results (WHO 2009b).

Secondary maternal outcomes

Maternal supplementation with a single postpartum dose of 200,000 to 300,000 IU vitamin A enhanced the**breast milk retinol** concentration at three to three and a half months postpartum, a more responsive indicator of vitamin A supplementation than serum retinol concentration (Stoltzfus 1993b). Moreover, serum retinol has some limitations as an indicator of vitamin A status, because retinol binding protein is a negative acute phase reactant protein (Filteau 1993; WHO 1996). Dancheck 2005 investigated the influence of acute phase reaction in breast milk retinol concentration in women from Malawi. The authors observed no significant differences in retinol concentration between lactating women with or without signs of inflammation. Thus, the meta-analyses of breast milk retinol in this review are probably more informative than serum retinol in assessing the impact of vitamin A supplementation.

There is concern that maternal administration of 400,000 IU in a single dose may cause a transient rise in breast milk retinoic acids and toxicity (Ross 2002). For this reason, the International Vitamin A Consultative Group (Ross 2002) recommends an interval of at least 24 hours between the two doses (200,000 IU each) for a total 400,000 IU vitamin A. Despite this recommendation, the full 400,000 IU was administered as one dose in two studies (ZVITAMBO Study Group; Ayah 2007), with no reports of breast milk retinoic acid concentration immediately after supplementation.

No included studies demonstrated differences in the proportion of those with signs or symptoms likely to be associated with the potential **adverse effects** from vitamin A supplementation, such as abdominal pain, vomiting, poor appetite, headaches, drowsiness, nausea or blurred vision.

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Although **serum retinol concentration** has some limitations as an indicator, the Global WHO database on VAD, a part of the Vitamin and Mineral Nutrition Information System (VMNIS), compiles data on the prevalence of clinical VAD (night blindness and ocular manifestation) and blood retinol concentration regularly from scientific literature and collaborators to estimate the prevalence of VAD around the world. These estimates provide valuable information for monitoring global progress and for evaluating current strategies to reduce VAD (WHO 2009b). The pooled analysis of the reviewed studies showed that maternal supplementation (200,000 to 300,000 IU) is associated with reduced proportions of low **vitamin A hepatic reserves** and significantly higher **serum retinol concentration** only until three months postpartum.

Primary infant outcomes

There was no evidence that postpartum maternal vitamin A supplementation influenced **infant mortality** in the five studies that each measured this outcome at different times (between two and 12 months) (Ayah 2007; Martins 2010; Newton 2005; Venkatarao 1996; ZVITAMBO Study Group). Only one small study included in the present review observed an impact on **infant morbidity** (duration of acute respiratory illness, number of febrile illnesses) (Roy 1997). Our results corroborate with the body of evidence presented in the systematic review by Gogia 2011, which observed no association between maternal and/or infant vitamin A supplementation on infant morbidity and mortality up to 12 months postpartum.

The coexistence of multiple micronutrient deficiencies could also be a factor that influenced the results. In a systematic review by Haider 2015 that assessed the effects of multiple-micronutrient supplementation for pregnant women, a significant decrease in the low birthweight, small-for-gestational age, and stillbirth rate was observed. Nonetheless, no beneficial impact on maternal, perinatal, or neonatal mortality was noted. Thus, further studies that consider fetal/neonatal/infant outcomes, as morbidities, following maternal multiple-micronutrient supplementation during pregnancy, breastfeeding, or both, may therefore be of interest.

Concern has been expressed about **adverse effects** from infant supplementation with high doses of vitamin A (more than 50,000 IU; Allen 2002), however studies included in this review did not report increased adverse signs and symptoms among infants after high-dose postpartum maternal supplementation.

Secondary infant outcomes

Regarding the**infant serum retinol** and **hepatic vitamin A reserves,** no protective effect of maternal vitamin A supplementation (200,000 to 400,000 IU) was observed (Ayah 2007, RETIBETA Project; Stoltzfus 1993a; WHO/CHD IVASSG).

A case-control study by Rondó 1997 conducted with Brazilian infants observed that cord blood retinol concentration was higher in infants with adequate growth for gestational age at the time of birth compared with infants with intrauterine growth restriction. According to the authors, one possible explanation for this result is maternal VAD. In our review, we included one study (Ayah 2007) that investigated the interaction of birthweight in the response to the vitamin A supplementation, but the authors found no evidence of effect. The studies included in this present systematic review did not provide data in a format that would allow us to perform subgroup analysis considering birthweight, although future studies may consider this.

The absence of effect can also be influenced by the low-quality control of the supplements. Only one study monitored the vitamin A content in the capsules during the trial and demonstrated that the vitamin content was stable in the capsules administered to the women. However, the lower-dose capsules administered to infants (results not included in this review) were subject to deterioration over time by up to 32% of expected content (Idindili 2007). Thus, the stability of vitamin A capsules should be considered in further studies and routine supplementation programmes (Idindili 2007; Newton 2008).

Supplement (vitamin A as retinyl) 400,000 IU versus 200,000 IU

A total of three studies (Darboe 2007; Fernandes 2012; Idindili 2007) evaluated the effects of two high doses of 200,000 IU vitamin A (400,000 IU) versus one dose (200,000 IU) and no improvements in maternal and infant health were observed. In these studies, women were supplemented with two doses of 200,000 IU with an interval of 24 hours, eight to 10 days, or one month, respectively, and no data regarding breast milk retinoic acid concentration were reported.

Overall completeness and applicability of evidence

We are confident that the search strategy was conducted in a robust and structured format to ensure capture of relevant studies for this review. The evidence was generated from studies that were conducted in areas of VAD (WHO 2009b). Even so, in most of the studies the baseline mean maternal serum concentrations were above the cut-off point proposed by WHO (WHO 1996). Despite this, our findings may be interpreted to represent chronic inadequate vitamin A reserves for women's health needs in these populations, which translated to infants born with inadequate reserves. This sub-optimal 'starting point' could not be corrected by postpartum administration of vitamin A to women, specifically when breastfeeding. Other systematic reviews of long-term supplementation to women during their reproductive years (including the postpartum period) and of infant supplementation may examine whether long-term preventive supplementation confers greater benefits than postpartum supplementation, that is, after the time when the infant has already received inadequate provision of vitamin A during pregnancy (Haider 2015; McCauley 2015). As noted by Sommer 2012, the limited evidence to date on the value of vitamin A supplementation needs to be further explored before widespread implementation of carotenoid supplementation.

Quality of the evidence

We judged the included trials to provide moderate- and low-quality evidence for the lack of differences in maternal and infant mortality, respectively; very low-quality evidence for maternal or infant morbidity; low-quality evidence for the lack of adverse effects of supplementation; and low-quality evidence that supplementation improved breast milk retinol levels (See: Summary of findings for the main comparison). The quality ratings were influenced by a number of factors, including the risk of bias: inadequate reporting of randomisation and allocation concealment or reasons for attrition. The studies were considered overall as being at low or unclear risk of bias, although some ratings of high risk were considered, for example where the control group was unblinded. Many of the studies enrolled small numbers, with few events, with

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wide 95% confidence intervals crossing the line of no effect and so were downgraded for imprecision. There was also some evidence of inconsistency as indicated by high statistical heterogeneity. In addition, some studies were sponsored by industry (or did not report funding) and undertook measures of mortality, morbidity and biological assays at a wide range of time points, limiting the potential for meta-analysis. However, we also judged that any bias was unlikely to have obscured a true effect of vitamin A (should it have existed).

Potential biases in the review process

We used several approaches in an attempt to minimise bias. The search strategy incorporated both the trials register of the Cochrane Pregnancy and Childbirth Group and other databases that were likely to include publications from less well-developed countries that may not be identified through standard searches. The review authors independently assessed eligibility for inclusion, conducted data extraction and negotiated on areas of concern or uncertainty. Considering the high number of meta-analyses, there is a risk of spuriously significant results.

Agreements and disagreements with other studies or reviews

Although the studies included in this review did not report increased adverse signs and symptoms among infants after high-dose postpartum maternal supplementation, the systematic review by Gogia 2011, reported that meta-analysis of two studies demonstrated an increase in the risk of bulging fontanelle after a second or third dose of vitamin A given directly to the infant. In view of this, future studies of maternal supplementation still need to consider the potential for this adverse effect that may be associated with cumulative or high doses of supplements.

AUTHORS' CONCLUSIONS

Implications for practice

In countries with widespread breastfeeding practices and high prevalences of vitamin A deficiency (VAD), the transient improvement in maternal serum retinol concentration and breast milk retinol represent at least a limited benefit of vitamin A supplementation for postpartum women. These findings need to be considered in the context of the potential for follow-up with longer-term supplementation to ultimately improve maternal and infant health outcomes.

No vitamin A supplementation regimens report adverse effects for women or their infants, in regions of VAD.

This review has not evaluated vitamin A supplementation in non-deficient populations.

Implications for research

This review's focus on postpartum supplementation needs to be considered as part of a wider focus on vitamin A status during infancy and for women, across their reproductive years, including the ideal dosing regimen to achieve improved maternal and infant health for those residing in countries of VAD, where there are also high rates of maternal and infant mortality. Moreover, the stability of vitamin A content in capsules needs consideration.

Further research may consider the potential interaction between vitamin A and other micronutrients, including iron and zinc. Other sustainable long-term strategies to achieve food and nutrition security, as increased access to local vitamin A rich foods, through agriculture- and nutrition-based interventions, and food and nutrition education, are also warranted.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ayah 2007

Methods	Randomised, double-blind, placebo-controlled, 2 by 2 factorial trial.
Participants	Women giving birth to a live single baby and their infants. Bondo, Kenya. N = 564 women and their infants.
Interventions	Single dosage administered to women within 24 hours of birth; single dosage to infant at 1-4 weeks of age. All infants received 100,000 IU vitamin A at 8 months of age (after trial). 4 intervention groups: 1. Women received 400,000 IU vitamin A and infant received 100,000 IU vitamin A as retinyl palmitate (n = 142). 2. Women received 400,000 IU vitamin A and infant received placebo (n = 140). 3. Women received placebo and infant received 100,000 IU vitamin A (n = 143). 4. Women received placebo and infant received placebo (n = 139).
Outcomes	Maternal serum and breast milk retinol concentrations. Infant serum retinol concentration and vitamin A hepatic stores (MRDR).
Notes	No information regarding breastfeeding pattern was provided. However, at least some breastfeeding is implied by the analysis of breast milk retinol at 6 months for 63% of the women originally enrolled. 87.4% of follow-up until 14 weeks, 77.1% of follow-up until 26 weeks postpartum.

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Ayah 2007 *(Continued)*

	The prevalence of HIV infection among antenatal attendees was above 28% at the time of the study. However, the trial was conducted prior to availability of HIV testing and anti-retrovirals for antenatal women in western Kenya. Thus, it was not possible to know the prevalence of HIV among recruited women. Sample size calculation reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Two random sequences of X and Y were prepared, one for the mothers and one for the infants. Identification numbers from 1 to 700 were assigned consecutively to each of the two lists and mother-infant pairs of capsules were packaged in zip-lock bags numbered from 1 to 700 and kept in batches of ten."
Allocation concealment (selection bias)	Low risk	"The randomisation codes were concealed for the entire trial duration and only revealed after completion of data analysis."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...prepared and supplied the vitamin A and identical-looking placebo supplements as oily capsules in brown bottles coded as X or Y."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The randomisation codes were concealed for the entire trial duration and only revealed after completion of data analysis."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were by ITT.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes reported.
Other bias	High risk	Supported by Hoffmann-La Roche Ltd (Basel Switzerland).

Bhaskaram 2000

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Hospital-based study with postpartum women who did not receive any vitamin A supplements during pregnancy and had uncomplicated full-term births. Hyderabad, India. N = 102 women and their infants.
Interventions	Single high dose to women within 24 hours after birth. 2 intervention groups: 1. Women received 200,000 IU vitamin A as retinyl palmitate (n = 50). 2. Women received placebo (n = 52).
Outcomes	Infant serum retinol concentration, corneal lesions and breast milk retinol concentration.
Notes	All infants given OPV within 72 hours after birth.

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Bhaskaram 2000 *(Continued)*

All infants breastfed, followed up at 6 months.

100% of follow-up until 6 weeks, 87% followed up until 3 months, 46% followed up until 6 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Vitamin A and placebo were coded by a person who had no connection with the investigation and the dose was administered by an auxiliary nurse midwife who was not aware of the code."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported, but outcomes (serum and breast milk retinol concentration) were unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for attrition and exclusions not reported. ITT analyses not performed.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes reported.
Other bias	Unclear risk	Source of funding not mentioned. No mention of any research protocol published a priori.

Darboe 2007

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Postpartum women without severe peripartum difficulties or preterm birth, with newborns ≥ 2200 g with no congenital defects at birth. Keneba and West Kiang, Gambia. N = 220 women and their infants.
Interventions	Single or double high dose to women at delivery (first dose) and within a week (second dose); and 3 high doses to infant at 2, 3 or 4 months. All infants received 100,000 IU vitamin A at 9 months and 200,000 IU at 12 months postpartum. 2 intervention groups: 1. Women received 400,000 IU vitamin A as retinyl palmitate and infant received 150,000 IU vitamin A (3 doses of 50,000 IU) (n = 110). 2. Women received 200,000 IU and infant received placebo (3 doses) (n = 110).
Outcomes	Maternal morbidity, serum and breast milk retinol concentrations. Infant morbidity, haemoglobin and serum retinol concentrations.

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Darboe 2007 *(Continued)*

Notes	No information regarding breastfeeding pattern was provided. However, at least partial breastfeeding is implied by the reported analysis of breast milk retinol to 6 months in 88% of those enrolled. 89.5% of follow-up until 12 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An independent senior scientist packed and labelled the supplements, and did a block randomisation procedure (16 per block) to allow for possible effects of season of birth."
Allocation concealment (selection bias)	Low risk	"All members of the trial team were unaware of allocation until the data had been cleaned and locked."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Vitamin A in vegetable oil and vegetable oil placebo were prepared by Hoffmann La Roche (Basel, Switzerland). An independent senior scientist packed and labelled the supplements, and did a block randomisation procedure (16 per block) to allow for possible effects of season of birth. Supplements or placebo were directly administered at home by field staff , apart from supplements at 2, 9, and 12 months, which were given at the clinic during follow-up. All members of the trial team were unaware of allocation until the data had been cleaned and locked."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“All members of the trial team were unaware of allocation until the data had been cleaned and locked.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition and exclusions were reported in detail, although ITT analysis was not performed.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes reported.
Other bias	Low risk	Trial registered a priori (No. ISRCTN 98554309). The UK Medical Research Council funded the study, and laboratory analyses in Coleraine were supported by BASF Aktiengesellschaft (Ludwigshafen, Germany).

Fernandes 2012

Methods	Randomised, triple-blind, placebo-controlled trial.
Participants	Women with 13 to 42 years of age, low obstetric risk, no gemelar and at-term gestation and their infants. Recife, Permambuco, Brazil. N = 312 pairs of women and infants.
Interventions	Single or double high dose to women at delivery (first dose) and within 8-10 days (second dose). 2 intervention groups:

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Fernandes 2012 *(Continued)*

	1. Women received 200,000 IU immediately postpartum + 200,000 IU vitamin A as retinyl palmitate at 8-10 postpartum (n = 152). 2. Mother received 200,000 IU vitamin A as retinyl palmitate immediately postpartum + placebo as soy oil capsules at 8-10 postpartum (n = 160). (All capsules had 40 mg vitamin E.)
Outcomes	Infant sides effects (vitamin A toxicity); duration and severity of episode of diarrhoea, fever, acute respiratory infection, otitis, VAD (signs of xerophthalmia), hospitalisations, severity signs (venous rehydration, antibiotic therapy) and serum retinol concentration. Maternal side effects (vitamin A toxicity), serum and breast milk retinol concentrations.
Notes	At least 60.45% of follow-up until 6 months. At least 70.6% of breastfeeding until 6 months. Registered at Clinical Trials: NCT00742937.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	”Mother–child pairs were assigned, through a simple randomization process by using a random number table into 2 treatment groups.” “[…] using a random number table generated by EPI INFO […]”
Allocation concealment (selection bias)	Low risk	“The randomization codes were kept secret during the whole study...”; “The placebo capsules had the same consistency, vehicle, coloration and flavour as the vitamin A capsules.”; "The research members were only informed of the allocation of the supplementation groups after the completion of data analysis.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules were used in the trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding was kept until end of the trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	"However, those who did not breastfeed their infants were not excluded from the study and received the normal follow-up for illness in their infants (i.e. follow-up was on an intention-to-treat basis).” "The nursing mothers who were not exclusively breastfeeding were not excluded from the research, and were still followed up and assessed based on the study design, that is, in terms of “intention to treat”." The authors probably performed an available-case ITT. It is possible to notice an imbalanced loss of follow-up comparing the arms. In the publication about breast milk; only 4-month data are reported.
Selective reporting (reporting bias)	High risk	Fetal growth as outcome in trial registration, only baseline data reported.
Other bias	High risk	In the 4 papers the authors reported different number of randomisation and baseline characteristics.

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Idindili 2007

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Women resident in the study area that brought their infants for vaccination. Ifakara, Tanzania. N = 780 women and their infants.
Interventions	Single or double high dose to women within 1 week after delivery; and 3 standard or higher doses to infant at 1, 2 or 3 months (DPT/OPV vaccination). All infants received 100,000 IU vitamin A at measles vaccination (9 months). 2 intervention groups: 1. Women received 200,000 IU vitamin A as retinyl palmitate and infant received 75 000 IU vitamin A (3 doses of 25 000 IU) (n = 390). 2. Women received 400,000 IU vitamin A and infant received 150,000 IU vitamin A (3 doses of 50,000 IU) (n = 390).
Outcomes	Infant morbidity, anaemia (packed cell volume), serum retinol concentration, vitamin A hepatic stores (MRDR) and breast milk retinol concentration.
Notes	At least 86% of infants were exclusively breastfed until 1 month. 81% of follow-up until 3 months; 79.5% until 6 months; and 77.2% until 9 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Individual randomization was achieved by using a list of study numbers that had been randomly assigned to an intervention arm in blocks of 10, generated by the Data and Safety Monitoring Board."
Allocation concealment (selection bias)	Low risk	"A compact disk containing the cleaned and locked database files was exchanged for the treatment randomization code, held by the Data and Safety Monitoring Board." All members of the trial team were unaware of allocation until the data had been cleaned and locked.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Vitamin A capsules providing different doses were manufactured by Accucaps Industries (Windsor, Canada) (25,000 and 50,000 IU) and RpScherer (Aprilia, Italy) (200,000 IU), and were supplied to the project by the WHO." Not enough detail to judge whether participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details were given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for attrition and exclusions not reported. ITT analyses not performed.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes reported.

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Idindili 2007 *(Continued)*

Other bias	Unclear risk	Post hoc analyses were conducted because of concerns that the capsules did not contain the necessary amount of vitamin A (in a sample of capsules vitamin degraded). Supported by Immunization Vaccines & Biologicals (the World Health Organization and the United Nations Foundation), Sight&Life (Hoffman-la Roche Ltd), Micronutrient Initiative, the Canadian International Development Agency, and the United Nations Children's Fund (UNICEF).

Martins 2010

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Women and their infants from a community attended at a Basic Health Unit. Ribeirão Preto, São Paulo, Brazil. N = 66 women and their infants.
Interventions	Single high dose to women between the 20 and 30th days postpartum compared with placebo. 2 intervention groups: 1. Women received 200,000 IU (retinyl palmitate) between the 20 and 30th days postpartum (n = 33). 2. Women received a placebo as soy oil capsules between the 20 and 30th days postpartum (n = 33).
Outcomes	Infant febrile and/or diarrhoeic episode during the preceding 15 days (collected from the medical records) and at 3 months of life and serum retinol concentration. Maternal serum and breast milk retinol concentrations.
Notes	89.39% of follow-up until 3 months. 75.4% of exclusive breastfeeding until 3 months. No trial register.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No explicit randomisation procedure reported. "[…] assigned at random […]".
Allocation concealment (selection bias)	Unclear risk	Not mentioned at all.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind trial" "who received identical capsules containing soy oil […]".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-blind trial", not specified, but reported outcomes unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Data analysis was based on intent to treat because the mothers who interrupted exclusive breast-feeding were not excluded."

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Martins 2010 *(Continued)*

		Similar missing data in both groups, dropout explained, available case ITT performed.
Selective reporting (reporting bias)	High risk	CRP levels only reported as baseline level. Febrile or diarrhoeic episodes not reported.
Other bias	Low risk	No other source of bias could be detected.

Newton 2005

Methods	Randomised, double-blind, placebo-controlled 2 x 2 factorial design trial.
Participants	Women 3-4 weeks postpartum and their infants. Kintampo, Brong Ahafo Region, Ghana. N = 1085 women and their infants.
Interventions	4 intervention groups: 1. Women received 200,000 IU of vitamin A as retinyl palmitate at 3-4 weeks and infant received total of 75,000 IU (25 000 IU at 6, 10 and 14 weeks) (n = 274). 2. Women received placebo at 3-4 weeks and infant received total of 75 000 IU (25,000 IU at 6, 10 and 14 weeks) (n = 265). 3. Women received 200,000 IU of vitamin A as retinyl palmitate and infant received total of placebo (n = 269). 4. Women received placebo and infant received placebo at 6, 10 and 14 weeks (n = 277).
Outcomes	Infant mortality, infant serum antibody titres for polio and tetanus at 6 months of age.
Notes	No information supplied regarding breastfeeding rates. The report's background outlined the evaluation of whether maternal supplementation alone could achieve adequate vitamin A status, without the need for infant supplementation. This suggests that women were breastfeeding. Infant supplementation linked to time of administration of diphtheria pertussis tetanus and polio vaccinations. It was confirmed with the first author that the mortality data in the study referred to infants.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Mothers and infants were allocated to 1 of 4 treatment groups, using a blocked randomization scheme."
Allocation concealment (selection bias)	Unclear risk	Details not provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The test and placebo capsules were identical in size colour and shape."

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Newton 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but outcomes were unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only infants of women for which blood sample was obtained in the end of the study were included in the analysis. Attrition was 34.6%.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes were reported.
Other bias	Unclear risk	Enrolment of participants was extended to higher than planned lost to follow-up. Sample size calculation provided, but unclear whether a protocol was published a priori. Supported by a grant from the Wellcome Trust.

RETIBETA Project

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Community-based study with women at 1-3 weeks after birth. Matlab, Bangladesh. N = 220 women and their infants.
Interventions	Single high dose to women within 1-3 weeks postpartum or beta-carotene daily for 9 months. 3 intervention groups: 1. Women received 200,000 IU of vitamin A as retinyl palmitate and placebo daily for 9 months postpartum (n = 74). 2. Women received placebo and 7.8 mg (1 300 µg RE or 4327 IU) of beta-carotene daily until 9 months postpartum (n = 73). 3. Women received placebo and placebo daily until 9 months postpartum (n = 73).
Outcomes	Maternl vitamin A hepatic stores (MRDR), serum and breast milk retinol concentrations. Infant serum retinol concentrations and vitamin A hepatic stores (MRDR), Both in a subsample of women and infants.
Notes	All Infants at least partially breastfed to 6 months of age. 87% ate complementary food during this period. 98% follow-up rates until 3 months, 95% until 6 months, and 92% until 9 months postpartum.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Before beginning the study, individual treatment codes and follow-up schedules were assigned to a sequence of identification numbers in blocks of 18 using a random number table"..."Each block contained all possible combinations of three treatment groups."
Allocation concealment (selection bias)	Low risk	"The study capsules were manufactured by Tischon Corporation (Salisbury, MD) and delivered to the field and to study participants coded as type A, B or C."

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RETIBETA Project *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules: packaged in blister pack strips. Vitamin A and placebo capsules differed in colour slightly - authors considered that foil packaging would reduce direct comparisons between groups. Beta-carotene and placebo capsules identical in colour.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specified, but outcomes were unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for attrition and exclusions not reported. ITT analyses not performed.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes were reported.
Other bias	Unclear risk	Supported by cooperative agreements between The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD, USA and the Office of Health and Nutrition, U.S. Agency for International Development, Washington, DC (DAN-5116-1-00-8051-00 and HRN-A-00-97-00015-00). Research protocol not published a priori.

Roy 1997

Methods	Randomised controlled trial.
Participants	Postpartum women. Dhaka, Bangladesh. N = 50 women and their infants.
Interventions	Single high dose to women within 24 hours after birth. 2 intervention groups: 1. Women received 200,000 IU vitamin A as retinyl palmitate plus 60 mg of iron daily for 9 months (n = 25). 2. Women received 60 mg of iron daily for 9 months (n = 25).
Outcomes	Maternal serum and breast milk retinol concentrations. Infant morbidity.
Notes	All babies were breastfed until 6 months postpartum. No information regarding breastfeeding pattern was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Women were randomly allocated to either the intervention or control group. No further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias)	High risk	Women in the control group did not receive a placebo.

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Roy 1997 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Field workers who assessed the outcomes were not aware of the objective of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were accounted for in the analysis.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes were reported.
Other bias	Unclear risk	Study supported by the International Centre for Diarrhoeal Disease Research and the United States Agency for International Development. Research protocol not published a priori.

Stoltzfus 1993a

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Women at 1-3 weeks postpartum. Java, Indonesia. N = 153 women and their infants.
Interventions	Single high dose to women within 1-3 weeks after birth. 2 intervention groups: 1. Women received 300,000 IU vitamin A as retinyl palmitate (n = 77). 2. Women received placebo (n = 76).
Outcomes	Maternal abnormal CIC, serum and breast milk retinol concentrations. Infant serum retinol concentration and vitamin A hepatic stores (RDR).
Notes	No specific information regarding breastfeeding pattern was provided. However, the report's title, background and analysis of breast milk retinol to 8 months postpartum strongly suggest that infants received at least some breast milk for the duration of the study. Additionally, it is noted that the 3 women who stopped breastfeeding were not included in the 6-month follow-up. 88.9% follow-up rate until 6 months postpartum.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Individual randomization to treatment codes A and B was done in blocks of eight according to the Moses-Oakford assignment algorithm."
Allocation concealment (selection bias)	Low risk	"The allocation of treatment codes A and B to vitamin A or placebo capsules was done by the Sight and Life Task Force, Hoffmann-LaRoche (Basel, Switzerland), who prepared the capsules."
Blinding of participants and personnel (performance bias)	Low risk	Vitamin A and placebo capsules "looked practically identical" and were prepared by "Sight and Life Task Force, Hoffmann-LaRoche" - in labelled foil packs.

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Stoltzfus 1993a *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All investigators, field and laboratory staff and study participants were blinded to the randomization code until field work was completed."
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for attrition and exclusions not reported. ITT analyses not performed.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes were reported.
Other bias	Unclear risk	Supported by a grant from the Thrasher Research Fund and a National Science Foundation Graduate Fellowship to Rebecca I. Stoltzfus. Study protocol not published a priori.

Venkatarao 1996

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Women at 1-2 weeks after birth. Tamil Nadu, India. N = 909 women and their infants.
Interventions	Single high dose to women within 1-2 weeks after birth and high dose to infant at 6 months . 3 intervention groups: 1. Women received 300,000 IU vitamin A as retinyl palmitate and Infant received 200,000 IU vitamin A (n = 301). 2. Women received 300,000 IU vitamin A and Infant received placebo (n = 297). 3. Women received placebo and Infant received placebo at 6 months of age (n = 311).
Outcomes	Infant morbidity and adverse effects.
Notes	99.7% of infants were breastfed for at least 6 months. No information regarding breastfeeding pattern was provided. 75.8% follow-up rate until 12 months postpartum.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomly allocated". No further details given.
Allocation concealment (selection bias)	Unclear risk	" the Medical Officer...administered the appropriate capsules to the mother from the sealed envelope supplied by the Statistical Section at the Camp Office."
Blinding of participants and personnel (performance bias)	Low risk	Capsules were "similar in colour". Infant syrup matched for colour and consistency.

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Venkatarao 1996 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors did not know about the intervention.
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusions and attrition were 23%. ITT analyses not performed.
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Source of funding not provided. No mention of research protocol.

Vinutha 2000

Methods	Randomised, controlled trial.
Participants	Postpartum women (primigravid and second-gravid). Mumbai, India. N = 109 women and their infants.
Interventions	Single high dose to women within 48 hours after delivery. 2 intervention groups: 1. Women received 200,000 IU vitamin A as Aquasol water-miscible (n = 53). 2. Women did not receive vitamin A or placebo (n = 56).
Outcomes	Maternal serum and breast milk retinol concentrations. Infant serum retinol concentration.
Notes	All babies were exclusively breastfed. 77.1% follow-up rate until 3 months postpartum.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised. No further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Women in the control group did not receive a placebo. No other details provided on blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Probably not blinded, but outcomes were unlikely to be influenced by blinding.

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Vinutha 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for attrition and exclusions not reported. ITT analyses not performed.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes were reported.
Other bias	Unclear risk	Funded by the Lokmanya Tilak Municipal Medical College and Hospital in Mumbai. Study protocol not published a priori.

WHO/CHD IVASSG

Methods	Randomised, double-blind, placebo-controlled, multicentre trial (India, Ghana, and Peru).
Participants	Postpartum women and their infants. New Delhi, India; Brong Ahafo, Ghana; Lima, Peru. N = 7078 women and their infants.
Interventions	Single high dose to women within 21-42 days after birth in Ghana and 18-28 days after birth in Peru and India. 3 doses to infant during their DPT or OPV immunization (6, 10, 14 weeks) in Ghana, India and (2, 3 and 4 months) in Peru. Multicentre trial - at 9 months, infants received 25,000 IU vitamin A with measles immunisation and infants from the control group received single high dose 100,000 IU vitamin A. Ghana trial - at 6 months, infants received 25,000 IU vitamin A and infants from the control group received single high dose 100,000 IU vitamin A. Multicentre trial - 2 intervention groups: 1. Women received 200,000 IU vitamin A as retinyl palmitate and Infants received 100,000 IU vitamin A (4 doses 25,000 IU) (n = 3522). 2. Women received placebo and Infants received placebo (3 doses) plus 100,000 IU vitamin A at 9 months (equivalent total dose received by group 1) (n = 3556). Ghana - 4 intervention groups: 1. Women received 200,000 IU vitamin A as retinyl palmitate and Infants received 100,000 IU vitamin A (4 doses 25,000 IU) (n = 196). 2. Women received placebo and Infants received vitamin A as per group 1 (n = 192). 3. Women received vitamin A as per group 1 and Infants received placebo at times of immunisation, plus 100,000 IU vitamin A at 6 months (equivalent total dose received by groups 1 and 2) (n = 185). 4. Women received placebo and Infants received placebo (3 doses), plus 100,000 IU vitamin A at 6 months (equivalent total dose received by groups 1 and 2) (n = 194).
Outcomes	Maternal serum and breast milk retinol concentrations. Infant mortality, morbidity, acute toxic effects, serum retinol concentration and vitamin A hepatic stores (MRDR).
Notes	At least 99.4% of infants were breastfed at enrolment. The sub-study that reported breast milk retinol gave these findings for 570 women, compared with 631 at 2 months, suggesting that the majority of infants were at least partially breastfed to 9 months. 74.9% follow-up rate until 12 months postpartum. Before and periodically during the study standardisation exercises to assess agreement within and between observers were conducted for the main outcome variables.

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WHO/CHD IVASSG *(Continued)*

	Standardisation across sites (Ghana, India and Peru) was ensured by exchange visits.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Identification numbers were generated by computer at the data management centre at John Hopkins University in Baltimore, and assigned as random permuted blocks of size eight."
Allocation concealment (selection bias)	Low risk	"Three sealed copies of study codes were prepared and kept at WHO in Geneva, with the ethics committee of the All India Institute of Medical Sciences in New Delhi, and at the data management centre in Baltimore. Access was limited to one data manager, who had no direct involvement in the data analysis, and who prepared information requested by the treatment effects monitoring committee."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The supplements and placebo, in identical opaque gelatin capsules, were packaged in individually coded blister packs in Baltimore."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All analyses were by intent to treat from the time of first administration of study capsule to the mother."
Selective reporting (reporting bias)	Low risk	All expected clinically relevant outcomes were reported.
Other bias	Low risk	Trial supported by the Child Health and Development Division of WHO, the Johns Hopkins Family Health and Child Survival Cooperative Agreement (HRN 5986-A-00-6006-00) with funding from the United States Agency for International Development, and the Indian Council of Medical Research. A study protocol was not mentioned but study described in detail.

ZVITAMBO Study Group

Methods	Randomised, double-blind, placebo-controlled, 2 by 2 factorial trial.
Participants	Postpartum women without a life-threatening condition and their infants with birthweight ≥ 1500 g from urban maternity centres. Harare, Zimbabwe. N = 14,110 women and their infants (n = 9562 HIV-negative women).
Interventions	Double high dose to women within 96 hours of birth and single high dose to infant. 4 treatment groups: 1. Women received 400,000 IU vitamin A as retinyl palmitate and infant received 50,000 IU vitamin A (n = 3529). 2. Women received 400,000 IU vitamin A and infant received placebo (n = 3529). 3. Women received placebo and infant received 50,000 IU vitamin A (n = 3530).

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ZVITAMBO Study Group *(Continued)*

	4. Women received placebo and infant received placebo (n = 3522).
Outcomes	Maternal mortality, morbidity, serum retinol concentration and haemoglobin concentration. Infant mortality, acute adverse effects (for 788 women-infant pairs only) and serum retinol concentration. Infant cause of death was determined from medical records when the death occurred in the hospital or from a review of verbal autopsy information by study paediatrician.
Notes	All women initiated breastfeeding (97% started breastfeeding within 12 hours postpartum). 99.5% were still breastfeeding at 6 months and 85.8% at 12 months postpartum.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A separate team at Johns Hopkins University prepared the study capsule packets. Study identification numbers were randomly allocated to the treatment groups by computer in blocks of 12. The numbers were printed on adhesive labels and affixed to amber-colored zip-lock plastic bags that were packed with the assigned capsules. Capsule packets were prepared separately for each of the 4 treatment groups and were then merged into numeric order before shipping to Zimbabwe, where a series of packets were distributed to each recruitment site. As each mother-infant pair was recruited, the capsules in the next sequential bag were administered, and the associated study number was assigned to the pair."
Allocation concealment (selection bias)	Low risk	"Lists linking the study number to the treatment were kept in sealed envelopes and encrypted computer files."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo and treatment capsules appeared identical. Preparation, randomisation and packing of capsules were performed at The Johns Hopkins University in the USA before shipping to HaTarea."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to intervention or control.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Only infants of mothers who remained HIV-negative to 12 months postpartum were included in the current analysis." Attrition was 11.3% (in both the vitamin A and placebo groups) for HIV-negative women (985/9562). Adverse event data were only available for a subset of 788 women-infant pairs. The analyses were not by ITT.
Selective reporting (reporting bias)	High risk	Not all clinically relevant outcomes were reported.
Other bias	Low risk	"The ZVITAMBO Project was primarily supported by the Canadian International Development Agency (R/C Project 690/M3688), the US Agency for International Development (cooperative agreement no. HRN-A-00-97-00015-00 between Johns Hopkins University and the Office of Health and Nutrition of the USAID), and a grant from the Bill and Melinda Gates Foundation (Seattle); additional support was provided by the Rockefeller Foundation (New York) and BASF (Ludwigshafen, Germany)."

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CIC: conjunctival impression cytology
CRP: C-reactive protein
DPT: diphtheria, pertussis, tetanus vaccine
ITT: intention-to-treat
IU: international unit
MRDR: modified relative dose response
OPV: oral polio vaccine
RE: Retinol equivalent
RDR: relative dose response
VAD: vitamin A deficiency

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmad 2009	Supplementation for women during pregnancy.
Ala-Houhala 1988	Alternate allocation to the intervention or control groups.
Alam 2010	Provision of fat rather than vitamin A supplements.
Atalhi 2011	Provision of vitamin A rich foods rather than vitamin A supplements.
Basu 2003	Alternate allocation to the intervention or control groups.
Bezerra 2009	Alternate allocation to the intervention or control groups.
Canfield 2001	Provision of vitamin A rich foods rather than vitamin A supplements.
De Pee 1995	Provision of vitamin A rich foods rather than vitamin A supplements.
El Hamdouchi 2013	Provision of vitamin A rich foods rather than vitamin A supplements.
Filteau 1999	Provision of vitamin A rich foods rather than vitamin A supplements.
Garcia 2010	Alternate allocation to the intervention or control groups.
Gossage 2000	Participants were lactating and non-lactating women (paired) who were then randomised to either supplement or placebo. The study was "designed to explore possible interactions between short-term β-carotene supplementation and lactation on mitogenic DNA synthesis in immune-related peripheral blood T lymphocytes as well as to determine the effects of β-carotene supplementation on concentrations of other major carotenoids in the plasma of lactating and nonlactating women." p.950. It was not designed to consider maternal or infant mortality or morbidity, where were the focus of our review.
Haskell 2013a	Supplementation after the first 6 weeks postpartum (4-12 months postpartum).
Haskell 2013b	Supplementation after the first 6 weeks postpartum (4-12 months postpartum).
Humphrey 2006	Vitamin A supplementation for women who live with HIV.
Khan 2007	Provision of vitamin A rich foods rather than vitamin A supplements.
Lietz 2001	Provision of vitamin A rich foods rather than vitamin A supplements.
Lietz 2006	Provision of vitamin A rich foods rather than vitamin A supplements.

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Study	Reason for exclusion
Lima 2012	Alternate allocation to the intervention or control groups.
Ncube 2001	Provision of vitamin A rich foods rather than vitamin A supplements.
NNIPS-2	Long-term supplementation for women of reproductive age.
ObaapaVitA	Long-term supplementation for women of reproductive age.
Swaminathan 2015	Provision of vitamin A rich foods and nutrition counselling rather than vitamin A supplements.
Tchum 2006	Alternate allocation to the control or test group.
Turner 2013	Supplementation after the first 6 weeks postpartum (4-12 months postpartum).
West 2011	Long-term supplementation for women of reproductive age.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Nga 2013

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Healthy women, 18 to 50 years of age, with no gemelar gestation. Hanoi, Vietnam. N = 400 women and their infants.
Interventions	1. Single high dose of vitamin A supplementation (200,000 IU) within 3 days plus a placebo at 6 weeks postpartum.* 2. A placebo within 3 days plus a single high dose of vitamin A supplementation (200,000 IU) at 6 weeks postpartum.*
Outcomes	Infant acute phase proteins (CRP, AGP), morbidities, nutritional status (anthropometry), hepatic vitamin A reserves and plasma retinol concentrations. Maternal acute phase proteins, serum and breast milk retinol concentrations.
Notes	We emailed the author questioning about the research publications and we received no answer. *As stated in the Clinical Trials Register. Registered at Clinical Trials Register: NCT00952640.

Wang 2012

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Healthy women, negative for Hepaptitis-B antigen, with no gemelar gestation, no complicated pregnancy, no breastfeeding restriction; infant with adequate newborn weight. Linyi, Shandong, China. N = 150 women and their infants.

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Wang 2012 *(Continued)*

Interventions	1. 2 high doses of vitamin A supplementation (200,000 IU) at 2 weeks and 3 months (total: 400,000 IU) postpartum plus daily doses of 10 mg alpha-tocopherol and 10 mcg cholecalciferol.* 2. Daily doses of vitamin A supplementation (4000 IU) plus daily doses of 10 mg alpha-tocopherol and 10 mcg cholecalciferol for 6 months during postpartum.* 3. No vitamin A supplementation plus daily doses of 10 mg alpha-tocopherol and 10 mcg cholecalciferol for 6 months during postpartum.*
Outcomes	Infant plasma anti hepatitis-B antibody, plasma retinol concentrations, plasma C-reactive protein and plasma alpha-acid glycoprotein. Maternal plasma and breast milk retinol concentrations.
Notes	We emailed the author questioning about the research publications and the answer was: "The experimental results you mentioned has not been published yet". *As stated in the protocol register. Chinese Clinical Trial Register: ChCTR-TRC-12001914.

AGP: alpha acid glycoprotein
CRP: C-reactive protein
IU: international unit

Characteristics of ongoing studies *[ordered by study ID]*

Ahmad 2015

Trial name or title	Stopping postpartum vitamin A supplementation: are we missing concealed benefit?
Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Pregnant women 18 to 32 years of age with low obstetric risk. Dhaka, Bangladesh. N = 128 women and their infants.
Interventions	1. Single high dose of vitamin A supplementation (200,000 IU) within 3 days plus a placebo at 6 weeks postpartum. 2. A placebo within 3 days plus single high dose of vitamin A supplementation (200,000 IU) at 6 weeks postpartum. 3. 2 high doses of vitamin A supplementation (200,000 IU) within 3 days and at 6 weeks (total: 400,000 IU) postpartum. 4. 2 placebos within 3 days and at 6 weeks postpartum.
Outcomes	Breast milk sIgA, sCD14, TGF-beta, IL-7, GM-CSF, maternal plasma and breast milk retinol concentrations. Microbial pattern recognition receptors (Toll-like receptor, TLR) and stimulated TNF-α, IL-10, and IFN-α responses; epitope-independent mitogen (PHA) stimulated T cell polarisation: IFN-γ (Th1), IL-13 (Th2), IL-17 (Th17), and IL-10 (Tr1); pertussis toxin and hepatitis B surface antigen-specific and IgG antibody-secreting plasma cell responses. Infant morbidities, anthropometry (growth and weight-for-age z-score) and plasma retinol concentration.
Starting date	October, 2013.
Contact information	smeahmad@icddrb.org
Notes	Clinical Trials Register: NCT02043223.

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IU: international unit

DATA AND ANALYSES

Comparison 1. Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality to 6 months	1	564	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.71]
1.1 400,000 IU versus placebo	1	564	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.09, 2.71]
2 Maternal fever at 3 months postpartum			Other data	No numeric data
2.1 200,000 IU versus no treatment			Other data	No numeric data
3 Maternal respiratory tract infection at 3 months postpartum			Other data	No numeric data
3.1 200,000 IU versus no treatment			Other data	No numeric data
4 Maternal diarrhoea at 3 months postpartum			Other data	No numeric data
4.1 200,000 IU versus no treatment			Other data	No numeric data
5 Maternal adverse effects of supplementation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Headache within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.74, 1.99]
5.2 Blurred vision within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.39, 6.82]
5.3 Drowsiness within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [0.91, 4.79]
5.4 Nausea within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.44, 4.31]
5.5 Vomiting within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.14]
5.6 Poor appetite within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [0.69, 7.14]
5.7 Abdominal pain within 30 hours of dosing: 400,000 IU versus placebo	1	786	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.95, 1.73]
6 Maternal serum retinol (mcmol/L) at 3 - 3.5 months postpartum	5		Mean Difference (IV, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 200,000 - 400,000 IU versus placebo or no treatment	5	704	Mean Difference (IV, Random, 95% CI)	0.11 [0.03, 0.19]
6.2 200,000 - 300,000 IU versus placebo or no treatment	4	302	Mean Difference (IV, Random, 95% CI)	0.17 [0.07, 0.26]
6.3 400,000 IU versus placebo	1	402	Mean Difference (IV, Random, 95% CI)	0.04 [-0.01, 0.09]
6.4 Beta-carotene: 7.8 mg daily versus placebo	1	54	Mean Difference (IV, Random, 95% CI)	0.10 [-0.14, 0.34]
7 Maternal serum retinol (mcmol/L) at 6 - 6.5 months postpartum	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 200,000 - 400,000 IU versus placebo or no treatment	4	533	Mean Difference (IV, Random, 95% CI)	0.06 [-0.06, 0.18]
7.2 200,000 - 300,000 IU versus placebo or no treatment	3	242	Mean Difference (IV, Random, 95% CI)	0.13 [0.03, 0.23]
7.3 400,000 IU versus placebo	1	291	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.08, 0.04]
7.4 Beta-carotene: 7.8 mg daily versus placebo	1	50	Mean Difference (IV, Random, 95% CI)	0.05 [-0.28, 0.38]
8 Maternal serum retinol (mcmol/L) at 9 months postpartum	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 200,000 - 300,000 IU versus placebo or no treatment	2	98	Mean Difference (IV, Random, 95% CI)	0.00 [-0.16, 0.17]
8.2 Beta-carotene: 7.8 mg daily versus placebo	1	51	Mean Difference (IV, Random, 95% CI)	0.19 [-0.08, 0.46]
9 Maternal low hepatic vitamin A reserves 3 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 200,000 - 300,000 IU versus placebo	2	191	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.16, 2.08]
9.2 Beta-carotene: 7.8 mg daily versus placebo	1	54	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.43, 1.32]
10 Maternal low hepatic vitamin A reserves 6 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 200,000 - 300,000 IU versus placebo	2	192	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.48, 2.23]
10.2 Beta-carotene: 7.8 mg daily versus placebo	1	50	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.21, 1.49]
11 Maternal low hepatic vitamin A reserves 9 months postpartum	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 200,000 IU versus placebo	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.29, 1.41]
11.2 Beta-carotene: 7.8 mg daily versus placebo	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.27, 1.30]
12 Maternal breast milk retinol (mcmol/L) at 3 - 3.5 months postpartum	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 200,000 - 400,000 IU versus placebo no treatment	6	837	Mean Difference (IV, Random, 95% CI)	0.20 [0.08, 0.31]
12.2 200,000 - 300,000 IU versus placebo no treatment	5	415	Mean Difference (IV, Random, 95% CI)	0.25 [0.12, 0.37]
12.3 400,000 IU versus placebo	1	422	Mean Difference (IV, Random, 95% CI)	0.08 [0.03, 0.13]
12.4 Beta-carotene: 7.8 mg daily versus placebo	1	109	Mean Difference (IV, Random, 95% CI)	0.02 [-0.17, 0.21]
13 Maternal breast milk retinol (mcmol/L) at 6 - 6.5 months postpartum	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 200,000 - 400,000 IU versus placebo or no treatment	4	645	Mean Difference (IV, Random, 95% CI)	0.20 [-0.01, 0.41]
13.2 200,000 - 300,000 IU versus placebo or no treatment	3	291	Mean Difference (IV, Random, 95% CI)	0.28 [-0.04, 0.60]
13.3 400,000 IU versus placebo	1	354	Mean Difference (IV, Random, 95% CI)	0.06 [0.01, 0.11]
13.4 Beta-carotene: 7.8 mg daily versus placebo	1	104	Mean Difference (IV, Random, 95% CI)	0.12 [-0.13, 0.37]
14 Maternal breast milk retinol (mcmol/L) at 8 - 9 months postpartum	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 200,000 - 300,000 IU versus placebo or no treatment	3	275	Mean Difference (IV, Random, 95% CI)	0.15 [-0.16, 0.45]
14.2 Beta-carotene: 7.8 mg daily versus placebo	1	103	Mean Difference (IV, Random, 95% CI)	0.21 [0.01, 0.41]
15 Maternal breast milk retinol (< 1.05 mcmol/L) at 3 months postpartum	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 200,000 - 300,000 IU versus placebo or no treatment	3	304	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.37, 0.84]
15.2 Beta-carotene: 7.8 mg daily versus placebo	1	109	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.15]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Maternal breast milk retinol (< 1.05 mcmol/L) at 6 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 200,000 - 300,000 IU versus placebo	2	241	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.22, 1.94]
16.2 Beta-carotene: 7.8 mg daily versus placebo	1	104	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.64, 1.10]
17 Maternal breast milk retinol (< 1.05 mcmol/L) at 8 - 9 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 200,000 - 300,000 IU versus placebo	2	225	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.45, 1.40]
17.2 Beta-carotene: 7.8mg daily versus placebo	1	103	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.03]
18 Maternal breast milk retinol (< 0.28 mcmol/g of fat) at 3 months postpartum	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 200,000 IU versus placebo	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.60, 1.07]
18.2 Beta-carotene: 7.8 mg daily versus placebo	1	109	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.29]
19 Maternal breast milk retinol (< 0.28 mcmol/g of fat) at 6 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 200,000 IU versus placebo	2	779	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
19.2 Beta-carotene: 7.8 mg daily versus placebo	1	104	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.12]
20 Maternal breast milk retinol (< 0.28 mcmol/g of fat) at 9 months postpartum	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 200,000 IU versus placebo	2	667	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.73, 1.04]
20.2 Beta-carotene: 7.8 mg daily versus placebo	1	102	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.60, 0.97]
21 Maternal abnormal conjunctival impression cytology 3 months postpartum	1	148	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.55, 1.80]
21.1 300,000 IU versus placebo	1	148	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.55, 1.80]
22 Maternal abnormal conjunctival impression cytology 6 months postpartum	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 300,000 IU versus placebo	1	142	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.17]
23 Infant mortality	5	6090	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.77, 1.52]
23.1 Deaths to 14 weeks: 400,000 IU versus placebo	1	279	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.33, 1.54]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.2 Deaths to 12 months: 300,000 IU versus placebo	1	598	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.34, 2.24]
23.3 Death to 6 months: 200,000 IU versus placebo	1	546	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.26, 9.17]
23.4 Deaths to 12 months: 400,000 IU versus placebo	1	4601	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.83, 1.98]
23.5 Deaths to 2 months: 200,000 IU versus placebo	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.90]
24 Infant diarrhoea (one or more episodes) to 12 months	1	456	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.06]
24.1 300,000 IU versus placebo	1	456	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.06]
25 Infant diarrhoea episodes and duration			Other data	No numeric data
25.1 200,000 IU versus no treatment			Other data	No numeric data
26 Infant gastroenteritis to 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 200,000 IU versus no treatment	1	84	Risk Ratio (M-H, Fixed, 95% CI)	6.03 [0.30, 121.82]
27 Infant acute respiratory infection (one or more episodes) to 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 300,000 IU versus placebo	1	456	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.03]
28 Infant upper respiratory tract infection to 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 200,000 IU versus treatment	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.22, 3.81]
29 Infant acute respiratory tract infection episodes and duration			Other data	No numeric data
29.1 200,000 IU versus no treatment			Other data	No numeric data
30 Infant febrile illness episodes			Other data	No numeric data
30.1 200,000 IU versus no treatment			Other data	No numeric data
31 Infant adverse effects of supplementation	1	444	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.61, 6.55]
31.1 Bulging fontanelle: 400,000 IU versus placebo	1	444	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.61, 6.55]
32 Infant serum retinol (mcmol/L) at 3 - 3.5 months postpartum	4		Mean Difference (IV, Random, 95% CI)	Subtotals only

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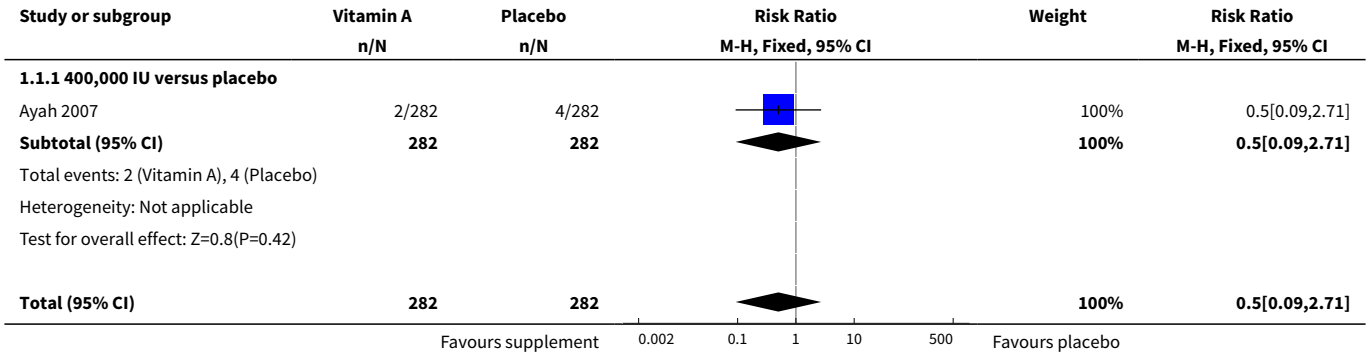
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
32.1 200,000 - 400,000 IU versus no treatment	4	379	Mean Difference (IV, Random, 95% CI)	0.11 [-0.05, 0.26]
32.2 200,000 IU versus placebo or no treatment	3	215	Mean Difference (IV, Random, 95% CI)	0.20 [0.00, 0.39]
32.3 400,000 IU versus placebo	1	164	Mean Difference (IV, Random, 95% CI)	0.02 [-0.03, 0.07]
33 Infant serum retinol (mcmol/L) at 6 - 6.5 months postpartum	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
33.1 200,000 - 400,000 IU versus placebo	4	430	Mean Difference (IV, Random, 95% CI)	0.04 [-0.00, 0.09]
33.2 200,000 - 300,000 IU versus placebo	3	289	Mean Difference (IV, Random, 95% CI)	0.03 [-0.02, 0.09]
33.3 Beta-carotene: 7.8 mg daily versus placebo	1	104	Mean Difference (IV, Random, 95% CI)	0.03 [-0.06, 0.12]
33.4 400,00 IU versus placebo	1	141	Mean Difference (IV, Random, 95% CI)	0.06 [-0.02, 0.14]
34 Infant low hepatic vitamin A reserves at 6 - 6.5 months postpartum	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
34.1 200,000 - 400,000 IU versus placebo	3	424	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.15]
34.2 200,000 - 300,000 IU versus placebo	2	235	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.22, 2.05]
34.3 400,000 IU versus placebo	1	189	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.90, 1.22]
34.4 Beta-carotene: 7.8 mg daily versus placebo	1	104	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.02]

Analysis 1.1. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 1 Maternal mortality to 6 months.



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Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 2 (Vitamin A), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.42)					

Analysis 1.2. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 2 Maternal fever at 3 months postpartum.

Maternal fever at 3 months postpartum

Study	Outcome	Supplement	Control	P value
200,000 IU versus no treatment				
Roy 1997	Number of cumulative episodes; (cumulative duration of illness in days)	10 (30); n = 25	10 (28); n = 25	Report states no significant difference

Analysis 1.3. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 3 Maternal respiratory tract infection at 3 months postpartum.

Maternal respiratory tract infection at 3 months postpartum

Study	Outcome	Supplement	Control	P value
200,000 IU versus no treatment				
Roy 1997	Number of cumulative episodes; (cumulative duration of illness in days)	23 (82); n = 25	25 (125); n = 25	Report states no significant difference
Roy 1997				

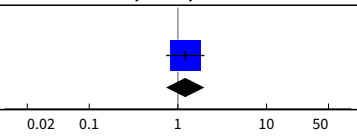
Analysis 1.4. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 4 Maternal diarrhoea at 3 months postpartum.

Maternal diarrhoea at 3 months postpartum

Study	Outcome	Vitamin A	Control	P value
200,000 IU versus no treatment				
Roy 1997	Number of cumulative episodes; (cumulative duration of illness in days)	10 (27); n = 25	2 (15); n = 25	Report states no significant difference

Analysis 1.5. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 5 Maternal adverse effects of supplementation.

Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Headache within 30 hours of dosing: 400,000 IU versus placebo					
ZVITAMBO Study Group	32/396	26/390		100%	1.21[0.74,1.99]
Subtotal (95% CI)	**396**	**390**		**100%**	**1.21[0.74,1.99]**



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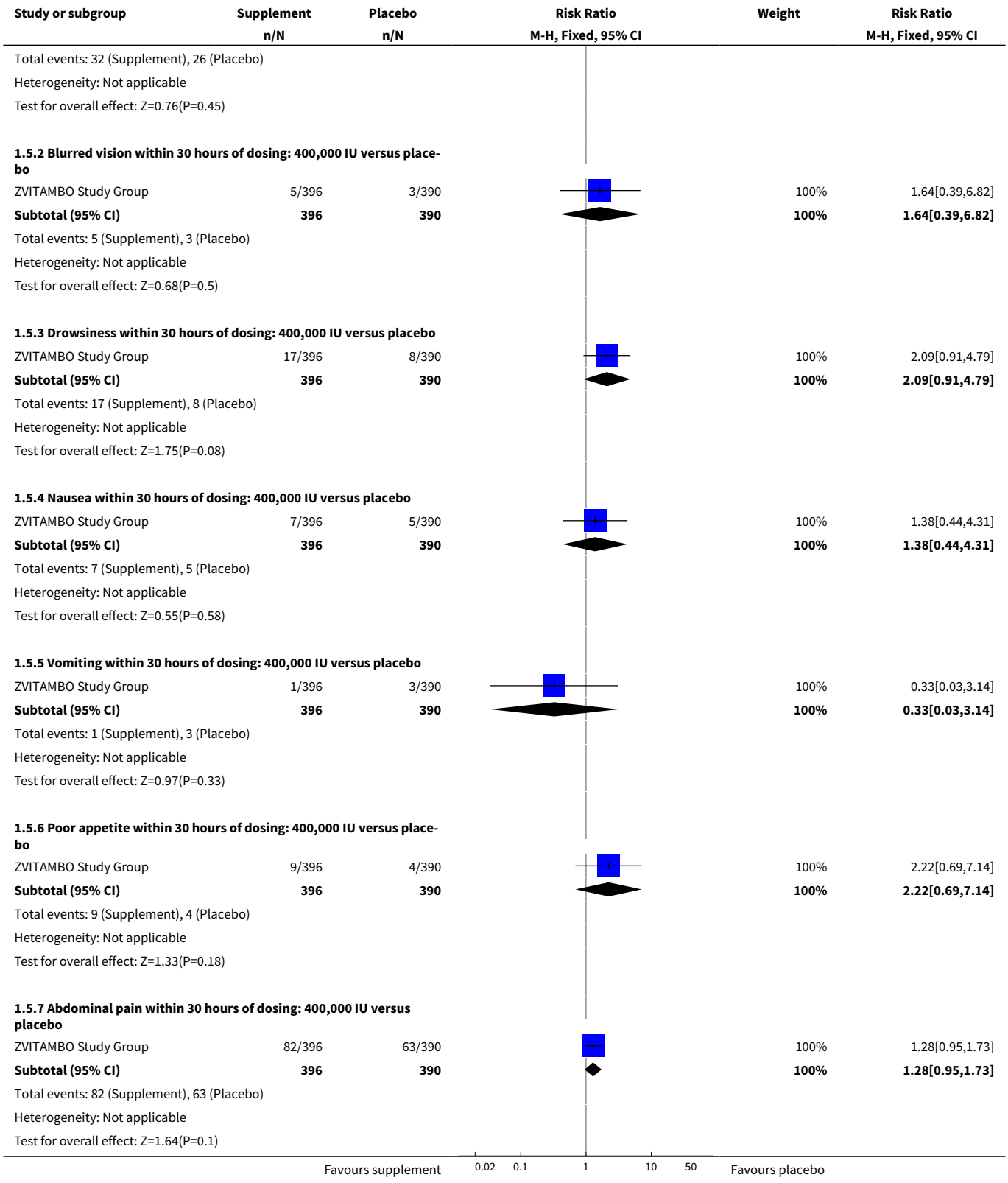

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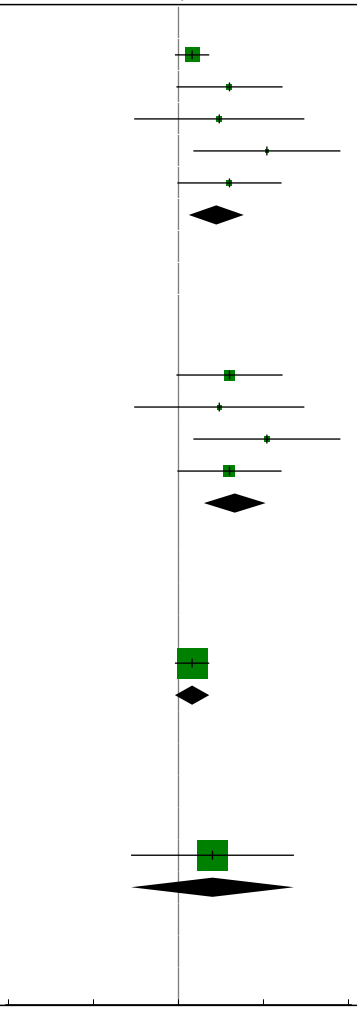
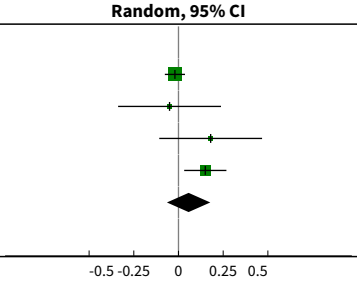
Analysis 1.6. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 6 Maternal serum retinol (mcmol/L) at 3 - 3.5 months postpartum.

Study or subgroup	Supplement N	Supplement Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 200,000 - 400,000 IU versus placebo or no treatment							
Ayah 2007	205	1.1 (0.2)	197	1 (0.3)		44.01%	0.04[-0.01,0.09]
Martins 2010	31	1.2 (0.3)	30	1 (0.3)		17.85%	0.15[-0.01,0.31]
RETIBETA Project	34	1.5 (0.5)	18	1.3 (0.4)		8.74%	0.12[-0.13,0.37]
Roy 1997	25	1.6 (0.4)	25	1.3 (0.4)		11.09%	0.26[0.04,0.48]
Stoltzfus 1993a	70	1.4 (0.5)	69	1.2 (0.4)		18.3%	0.15[-0,0.3]
Subtotal ***	**365**		**339**			**100%**	**0.11[0.03,0.19]**
Heterogeneity: Tau^2=0; Chi^2=6.53, df=4(P=0.16); I^2=38.78%							
Test for overall effect: Z=2.69(P=0.01)							
1.6.2 200,000 - 300,000 IU versus placebo or no treatment							
Martins 2010	31	1.2 (0.3)	30	1 (0.3)		33.92%	0.15[-0.01,0.31]
RETIBETA Project	34	1.5 (0.5)	18	1.3 (0.4)		13.2%	0.12[-0.13,0.37]
Roy 1997	25	1.6 (0.4)	25	1.3 (0.4)		17.68%	0.26[0.04,0.48]
Stoltzfus 1993a	70	1.4 (0.5)	69	1.2 (0.4)		35.21%	0.15[-0,0.3]
Subtotal ***	**160**		**142**			**100%**	**0.17[0.07,0.26]**
Heterogeneity: Tau^2=0; Chi^2=0.94, df=3(P=0.82); I^2=0%							
Test for overall effect: Z=3.57(P=0)							
1.6.3 400,000 IU versus placebo							
Ayah 2007	205	1.1 (0.2)	197	1 (0.3)		100%	0.04[-0.01,0.09]
Subtotal ***	**205**		**197**			**100%**	**0.04[-0.01,0.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.55(P=0.12)							
1.6.4 Beta-carotene: 7.8 mg daily versus placebo							
RETIBETA Project	36	1.4 (0.4)	18	1.3 (0.4)		100%	0.1[-0.14,0.34]
Subtotal ***	**36**		**18**			**100%**	**0.1[-0.14,0.34]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.82(P=0.41)							
Test for subgroup differences: Chi^2=6.41, df=1 (P=0.09), I^2=53.17%							



Analysis 1.7. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 7 Maternal serum retinol (mcmol/L) at 6 - 6.5 months postpartum.

Study or subgroup	Supplement N	Supplement Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.7.1 200,000 - 400,000 IU versus placebo or no treatment							
Ayah 2007	148	1 (0.3)	143	1 (0.2)		42.1%	-0.02[-0.08,0.04]
RETIBETA Project	35	1.5 (0.4)	18	1.5 (0.6)		12.85%	-0.05[-0.34,0.24]
Roy 1997	25	1.5 (0.7)	25	1.4 (0.3)		12.86%	0.18[-0.11,0.47]
Stoltzfus 1993a	67	1.2 (0.3)	72	1.1 (0.4)		32.19%	0.15[0.03,0.27]
Subtotal ***	**275**		**258**			**100%**	**0.06[-0.06,0.18]**
Heterogeneity: Tau^2=0.01; Chi^2=7.97, df=3(P=0.05); I^2=62.36%							



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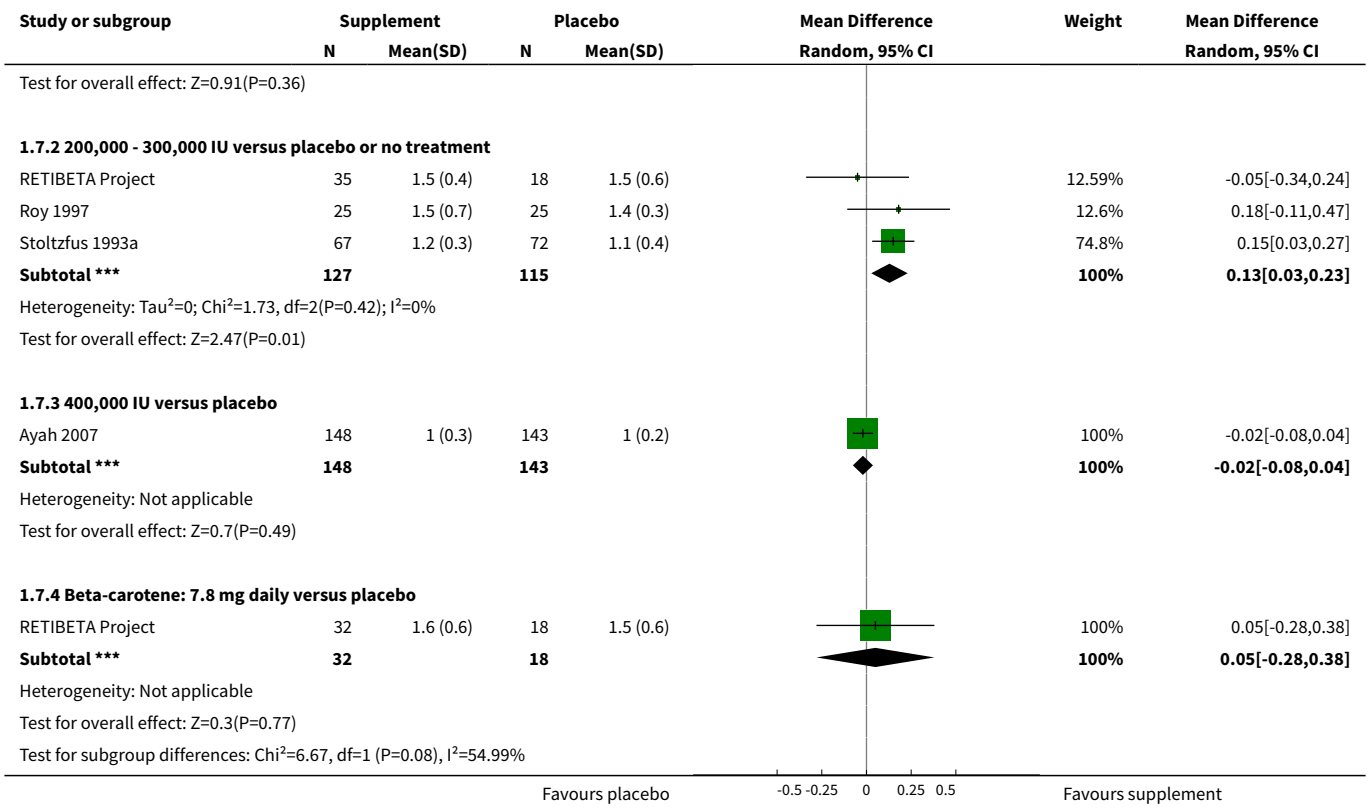
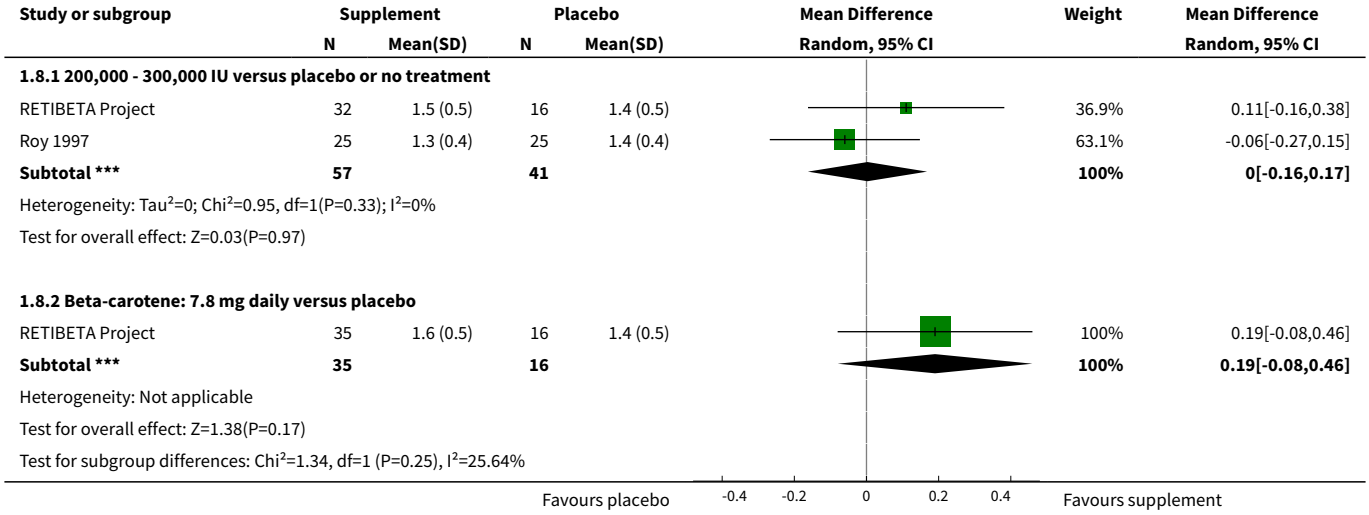


Analysis 1.8. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 8 Maternal serum retinol (mcmol/L) at 9 months postpartum.



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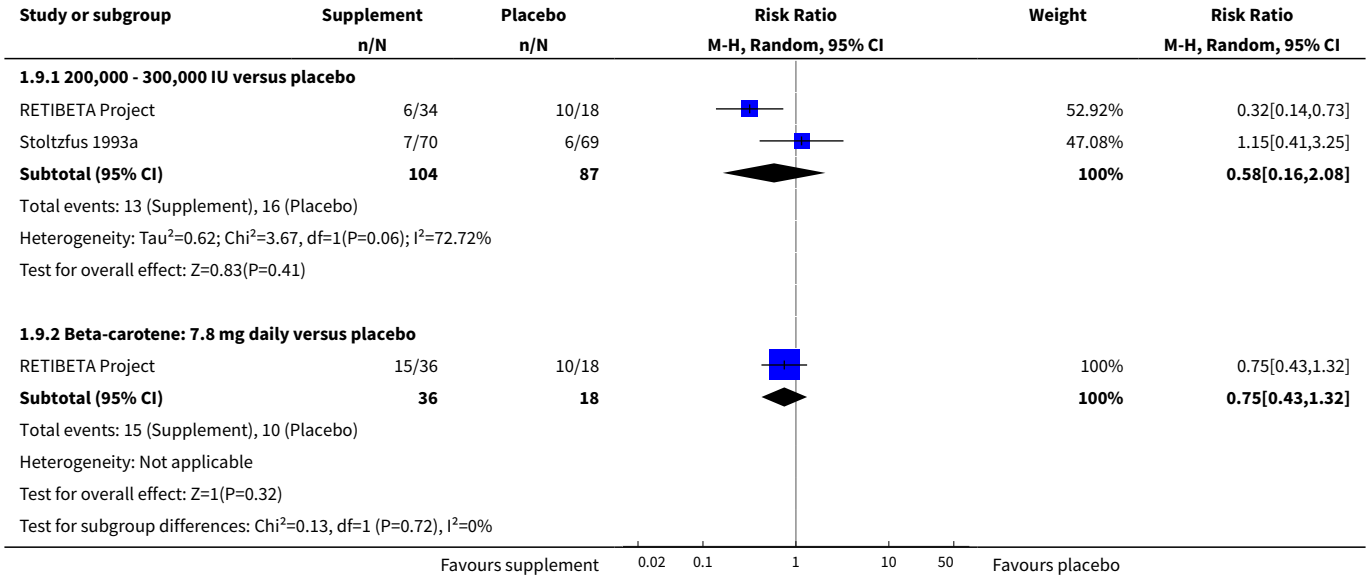
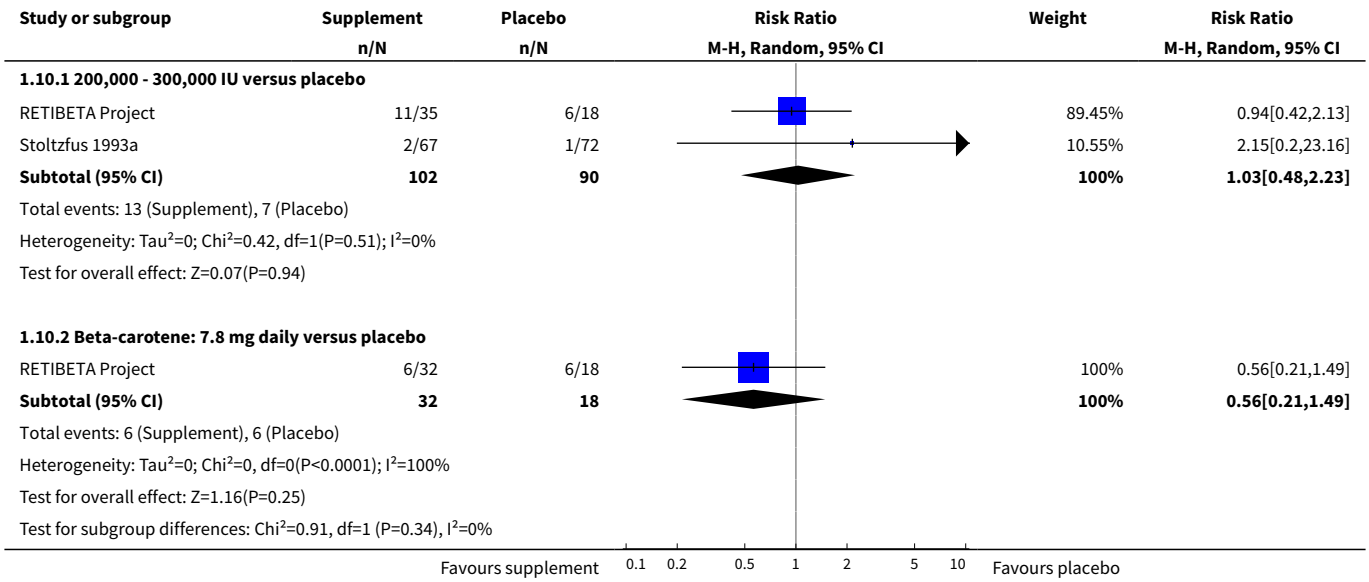
Analysis 1.9. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 9 Maternal low hepatic vitamin A reserves 3 months postpartum.



Analysis 1.10. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 10 Maternal low hepatic vitamin A reserves 6 months postpartum.



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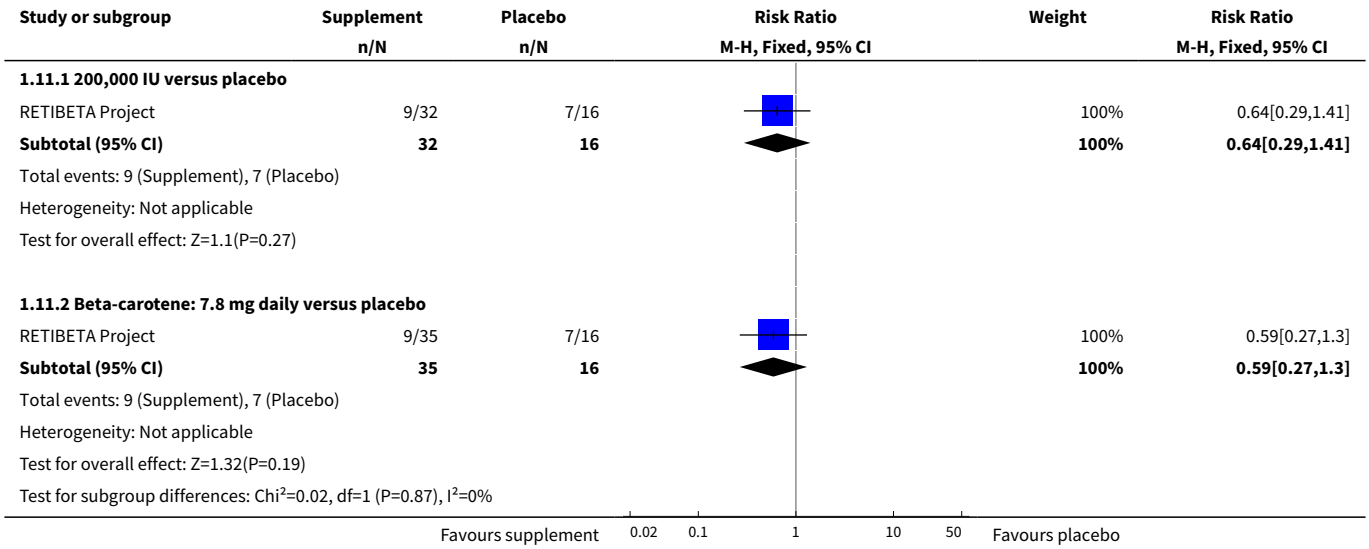
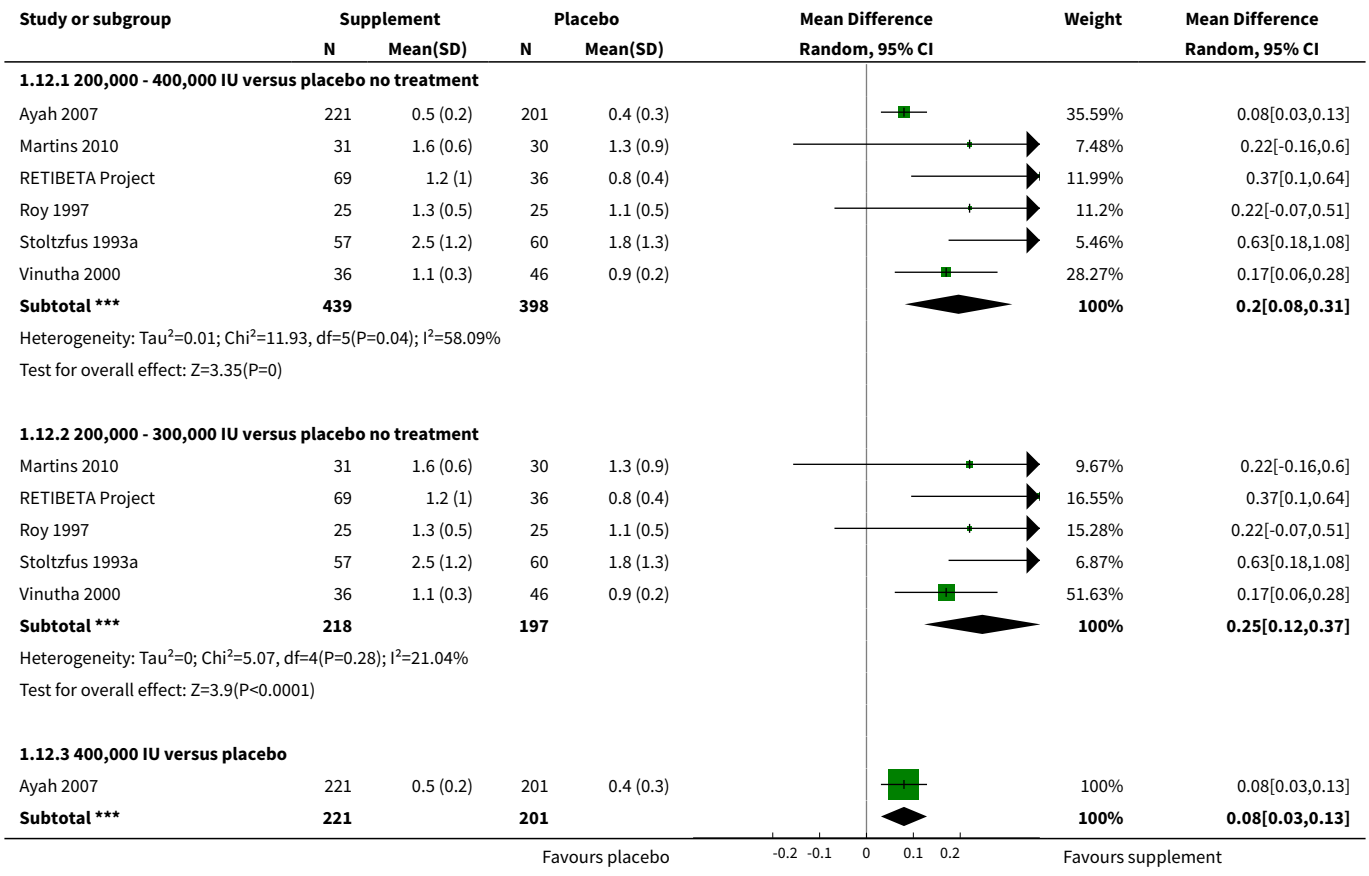
Analysis 1.11. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 11 Maternal low hepatic vitamin A reserves 9 months postpartum.



Analysis 1.12. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 12 Maternal breast milk retinol (mcmol/L) at 3 - 3.5 months postpartum.



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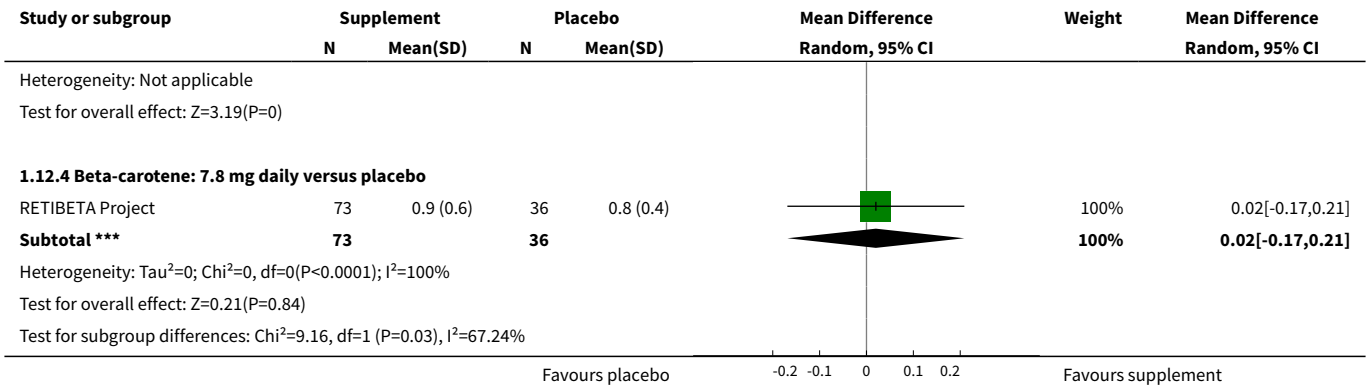
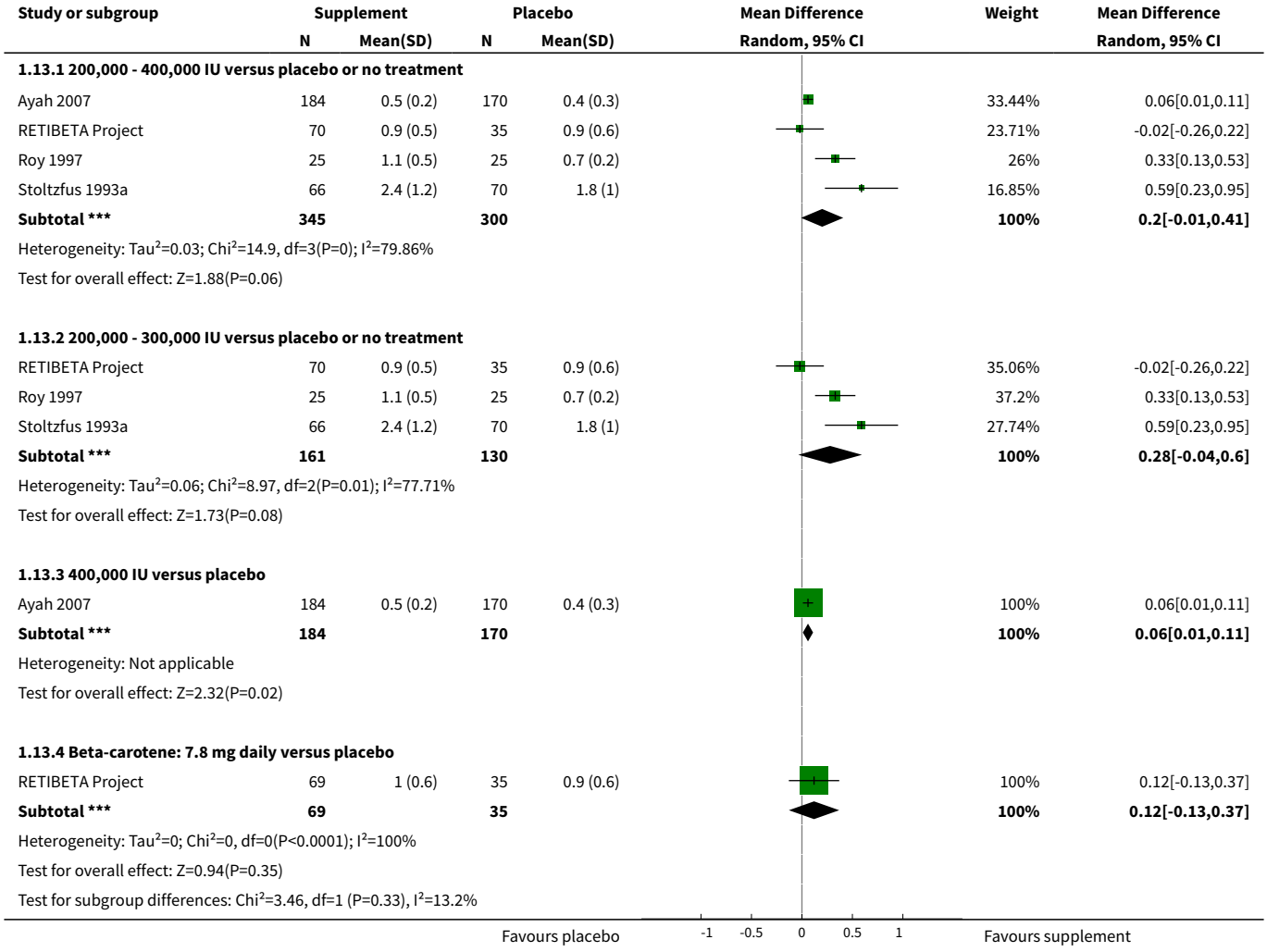


Analysis 1.13. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 13 Maternal breast milk retinol (mcmol/L) at 6 - 6.5 months postpartum.



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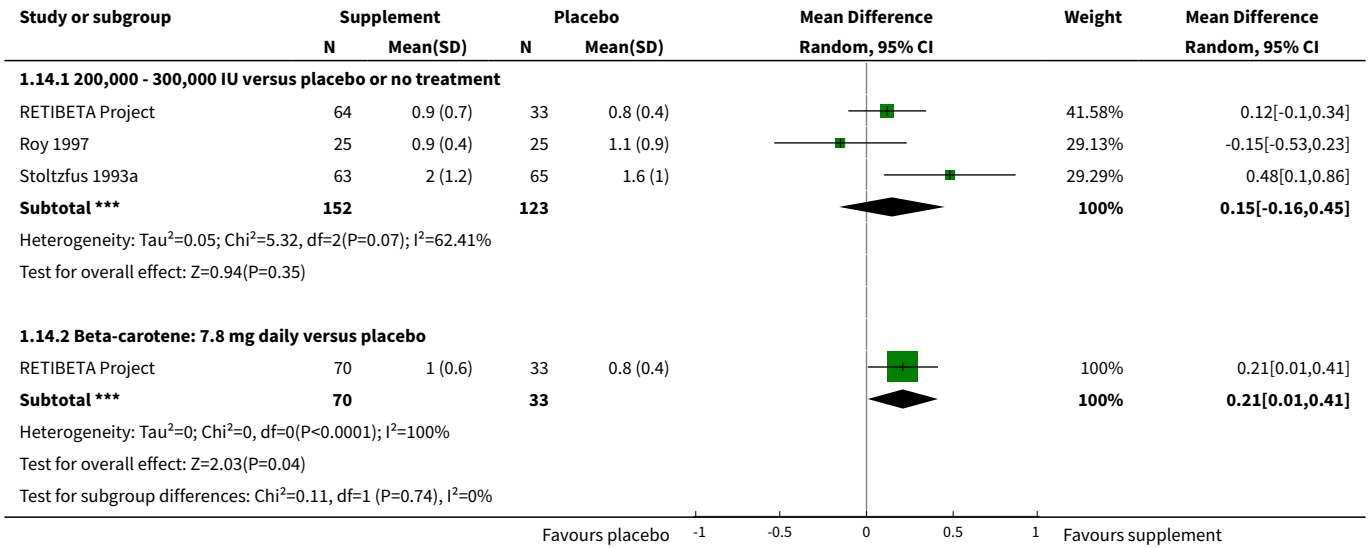
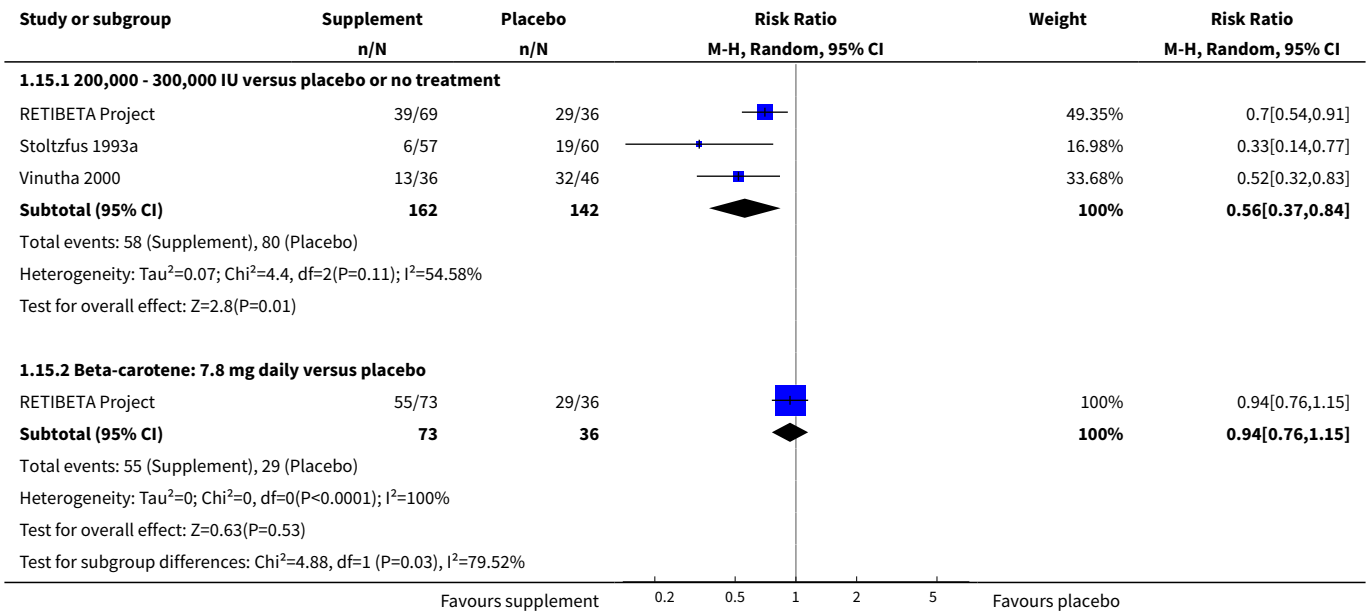
Analysis 1.14. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 14 Maternal breast milk retinol (mcmol/L) at 8 - 9 months postpartum.



Analysis 1.15. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 15 Maternal breast milk retinol (< 1.05 mcmol/L) at 3 months postpartum.



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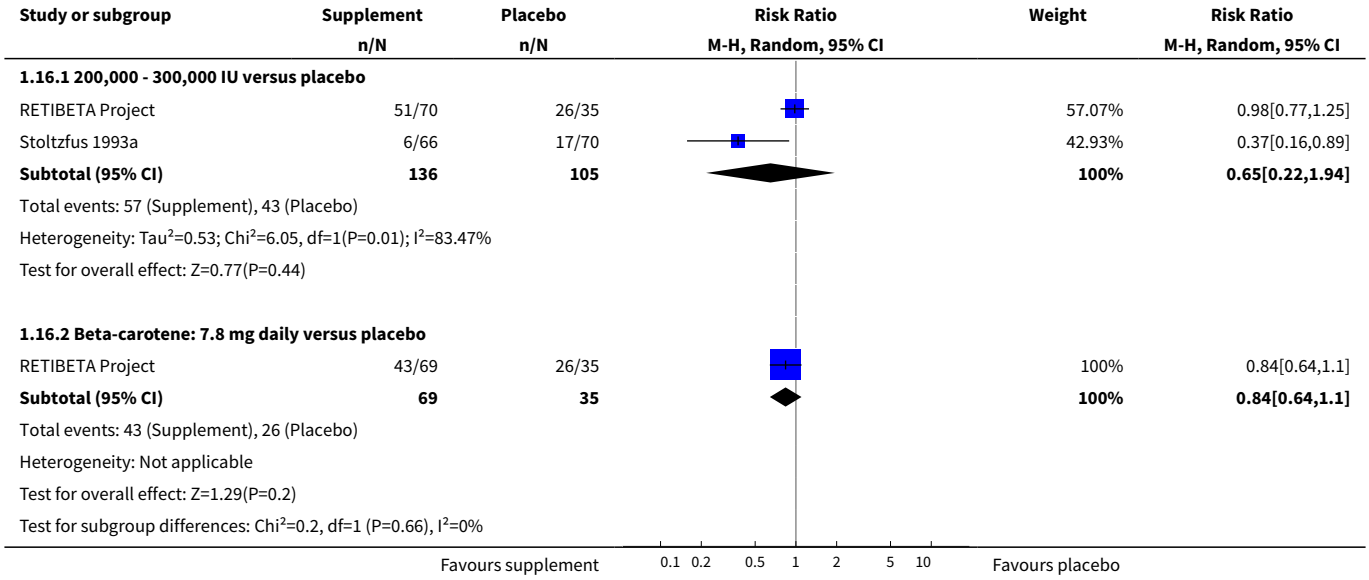
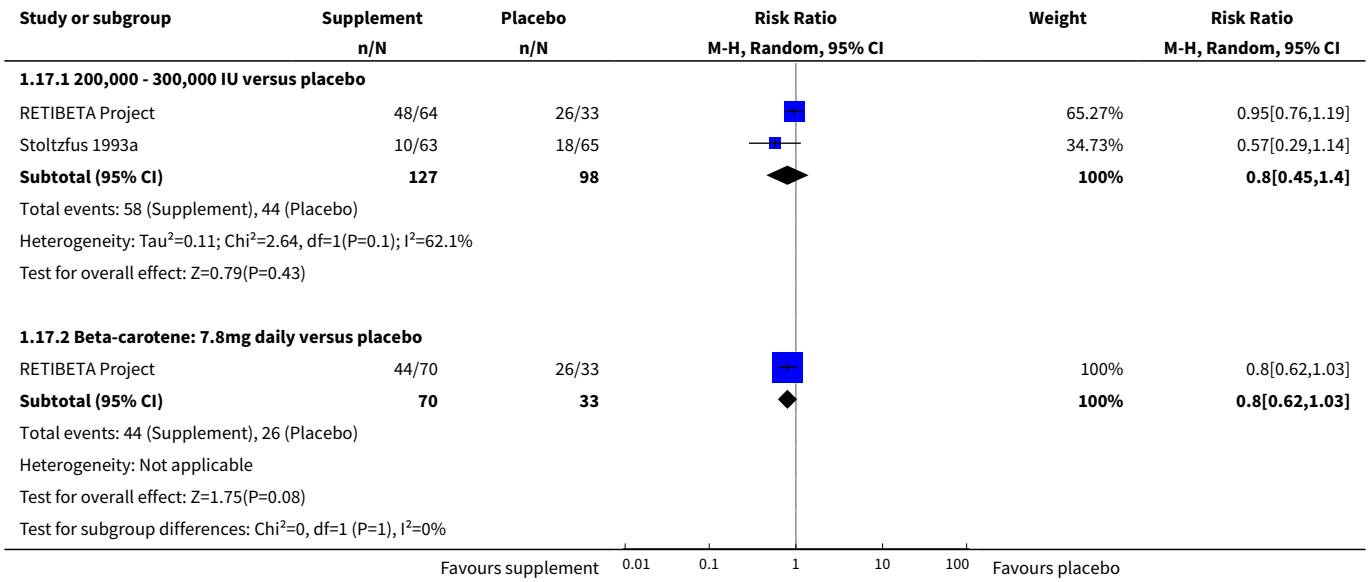
Analysis 1.16. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 16 Maternal breast milk retinol (< 1.05 mcmol/L) at 6 months postpartum.



Analysis 1.17. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 17 Maternal breast milk retinol (< 1.05 mcmol/L) at 8 - 9 months postpartum.



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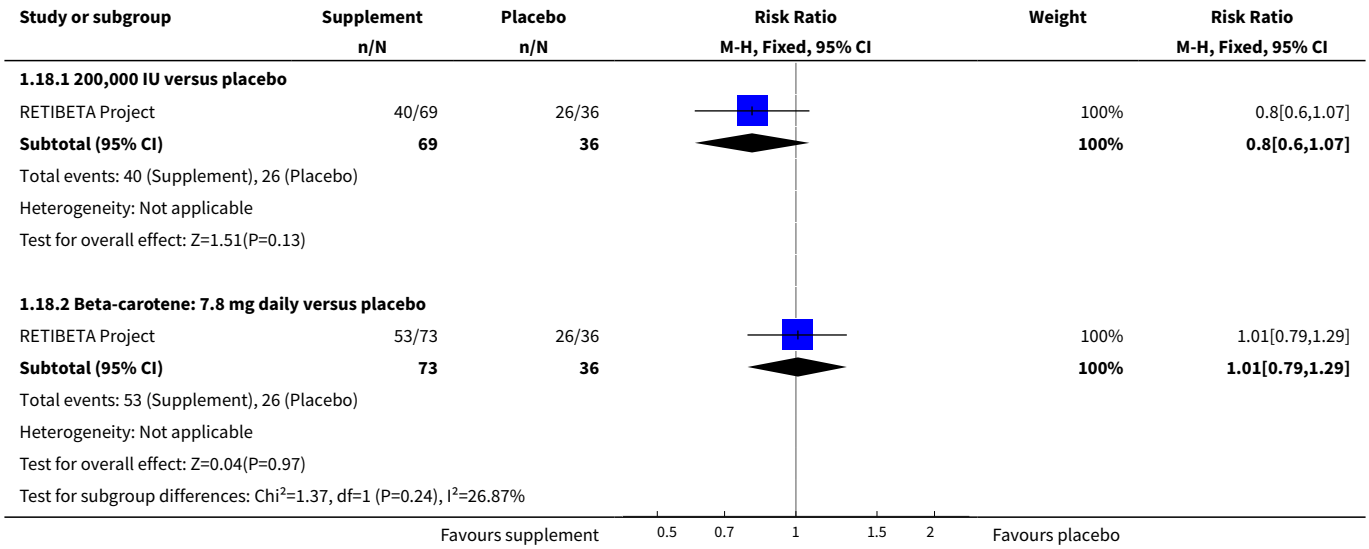
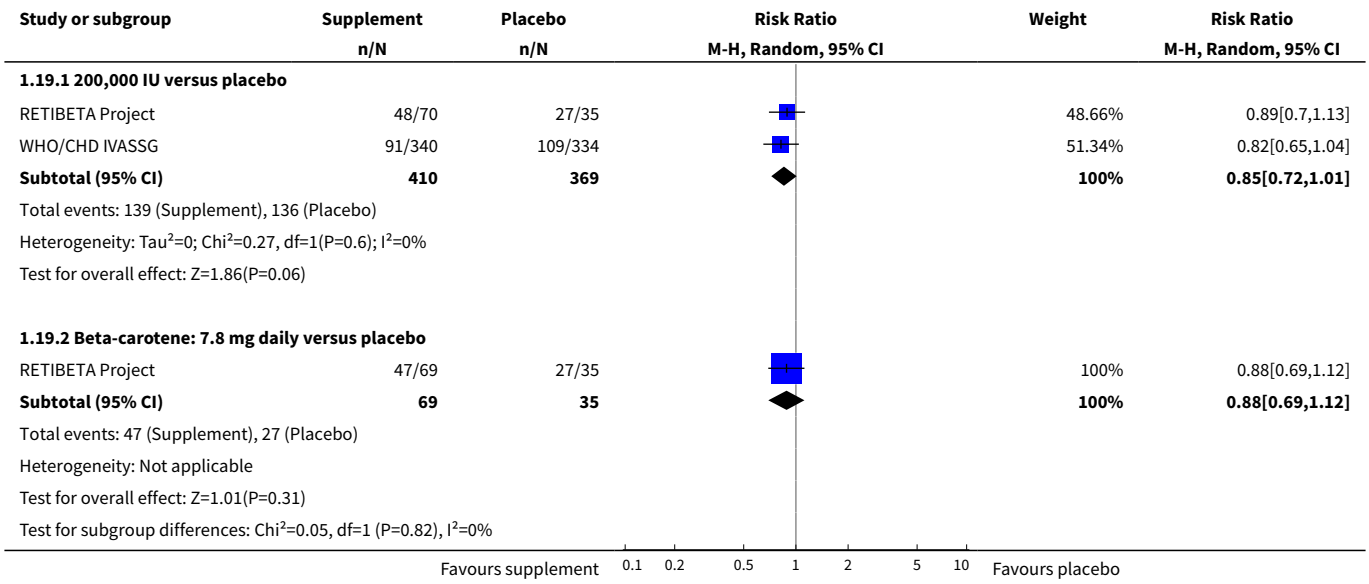
Analysis 1.18. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 18 Maternal breast milk retinol (< 0.28 mcmol/g of fat) at 3 months postpartum.



Analysis 1.19. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 19 Maternal breast milk retinol (< 0.28 mcmol/g of fat) at 6 months postpartum.



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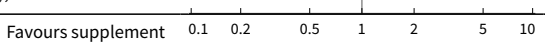
Analysis 1.20. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 20 Maternal breast milk retinol (< 0.28 mcmol/g of fat) at 9 months postpartum.

Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 200,000 IU versus placebo					
RETIBETA Project	43/64	27/33		55.29%	0.82[0.65,1.04]
WHO/CHD IVASSG	76/276	86/294		44.71%	0.94[0.72,1.22]
Subtotal (95% CI)	**340**	**327**		**100%**	**0.87[0.73,1.04]**
Total events: 119 (Supplement), 113 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=1.53(P=0.13)					
1.20.2 Beta-carotene: 7.8 mg daily versus placebo					
RETIBETA Project	43/69	27/33		100%	0.76[0.6,0.97]
Subtotal (95% CI)	**69**	**33**		**100%**	**0.76[0.6,0.97]**
Total events: 43 (Supplement), 27 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.19(P=0.03)					
Test for subgroup differences: Chi^2=0.79, df=1 (P=0.37), I^2=0%					

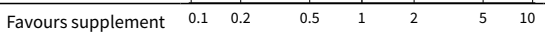


Analysis 1.21. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 21 Maternal abnormal conjunctival impression cytology 3 months postpartum.

Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.21.1 300,000 IU versus placebo					
Stoltzfus 1993a	17/74	17/74		100%	1[0.55,1.8]
Subtotal (95% CI)	**74**	**74**		**100%**	**1[0.55,1.8]**
Total events: 17 (Supplement), 17 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**74**	**74**		**100%**	**1[0.55,1.8]**
Total events: 17 (Supplement), 17 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 1.22. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 22 Maternal abnormal conjunctival impression cytology 6 months postpartum.

Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.22.1 300,000 IU versus placebo					



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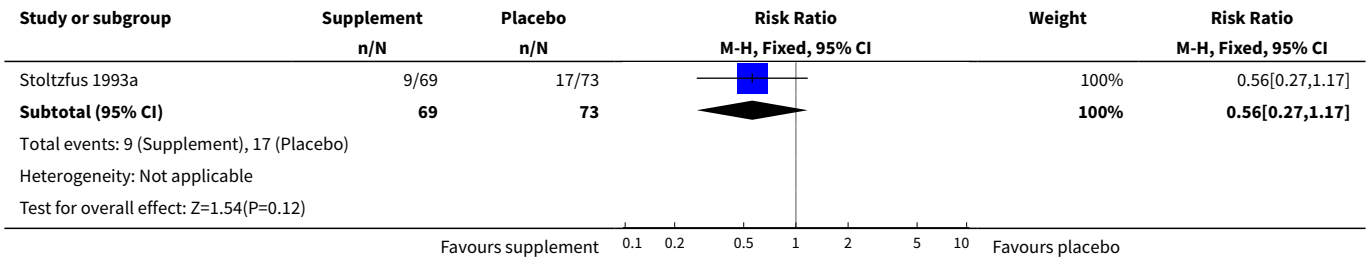
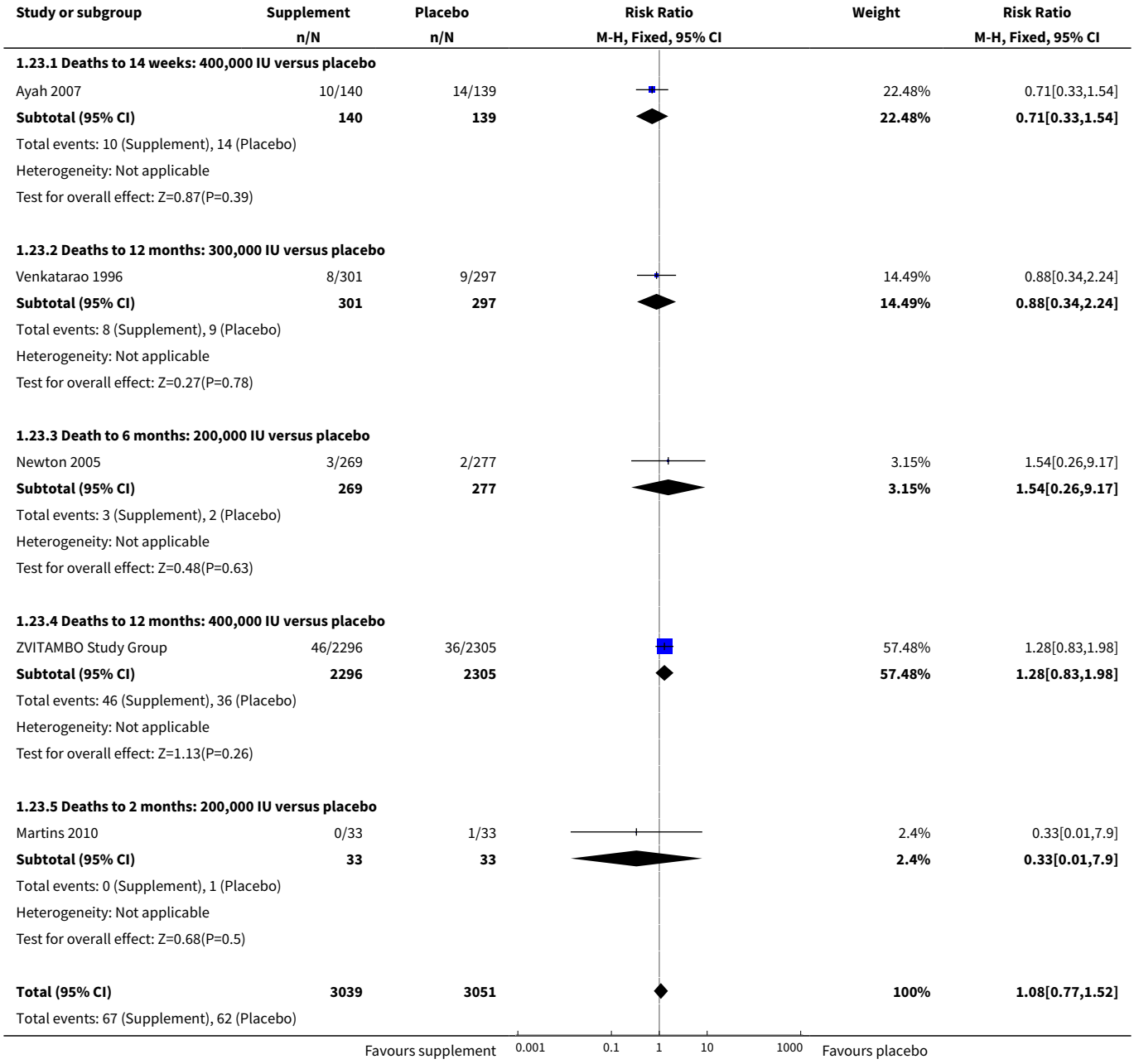


Analysis 1.23. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 23 Infant mortality.



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Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=2.61, df=4(P=0.63); I²=0%					
Test for overall effect: Z=0.45(P=0.65)					
Test for subgroup differences: Chi²=2.61, df=1 (P=0.63), I²=0%					

Favours supplement 0.001 0.1 1 10 1000 Favours placebo

Analysis 1.24. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 24 Infant diarrhoea (one or more episodes) to 12 months.

Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.24.1 300,000 IU versus placebo					
Venkatarao 1996	221/228	216/228		100%	1.02[0.98,1.06]
Subtotal (95% CI)	**228**	**228**		**100%**	**1.02[0.98,1.06]**
Total events: 221 (Supplement), 216 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.17(P=0.24)					
Total (95% CI)	**228**	**228**		**100%**	**1.02[0.98,1.06]**
Total events: 221 (Supplement), 216 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.17(P=0.24)					

Favours supplement 0.5 0.7 1 1.5 2 Favours control

Analysis 1.25. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 25 Infant diarrhoea episodes and duration.

		Infant diarrhoea episodes and duration		
Study	**Outcome**	**Supplement**	**No treatment**	**Significance**
		200,000 IU versus no treatment		
Roy 1997	Diarrhoea episodes (mean episodes per child-week of observation)	0.12 (95% CI 0.09 to 0.15)	0.11 (95% CI 0.08 to 0.14)	P = 0.59
Roy 1997	Diarrhoea duration (duration (days) per child-week of observation)	0.74 (95% CI 0.53 to 0.95)	0.71 (95% CI 0.50 to 0.92)	P = 0.78
Roy 1997	Child-weeks	515	522	

Analysis 1.26. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 26 Infant gastroenteritis to 3 months.

Study or subgroup	Supplement n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.26.1 200,000 IU versus no treatment					
Vinutha 2000	2/38	0/46		100%	6.03[0.3,121.82]
Subtotal (95% CI)	**38**	**46**		**100%**	**6.03[0.3,121.82]**
Total events: 2 (Supplement), 0 (Control)					

Favours supplement 0.05 0.2 1 5 20 Favours control

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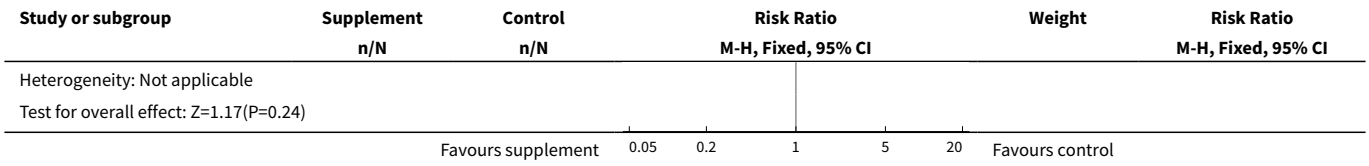
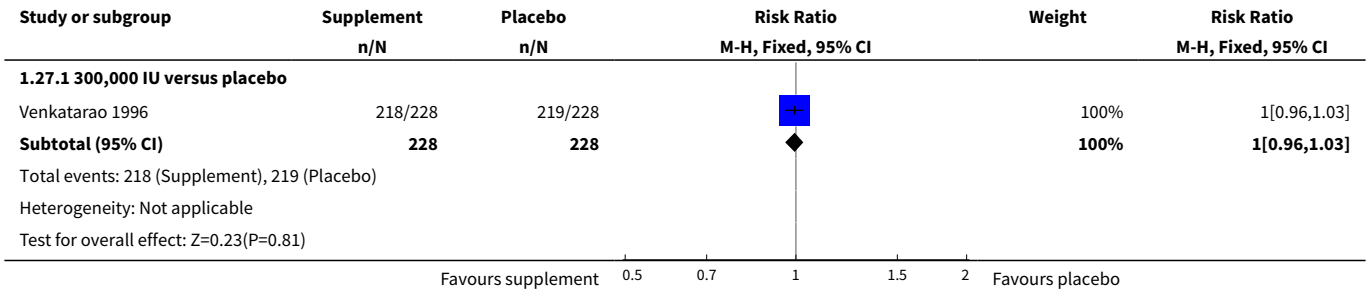
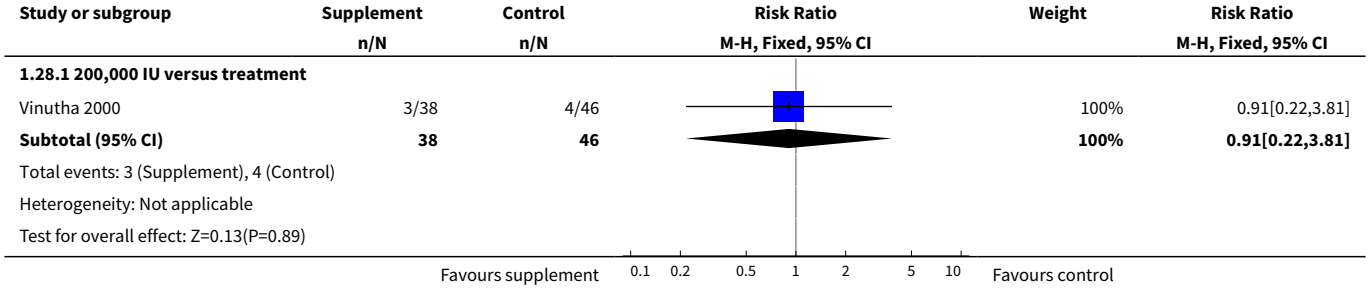


Analysis 1.27. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 27 Infant acute respiratory infection (one or more episodes) to 12 months.



Analysis 1.28. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 28 Infant upper respiratory tract infection to 3 months.



Analysis 1.29. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 29 Infant acute respiratory tract infection episodes and duration.

Infant acute respiratory tract infection episodes and duration				
Study	**Outcome / Details**	**Vitamin A**	**Control**	**Significance**
		200,000 IU versus no treatment		
Roy 1997	Acute respiratory tract infection episodes (mean episodes per child-week of observation)	0.42 (95% CI 0.38 to 0.46)	0.45 (95% CI 0.41 to 0.49)	P = 0.51
Roy 1997	Acute respiratory tract infection duration (duration (days) per child-week of observation)	3.1 (95% CI 2.7 to 3.5)	3.7 (95% CI 3.25 to 4.15)	P = 0.03
Roy 1997	Child-weeks	515	522	

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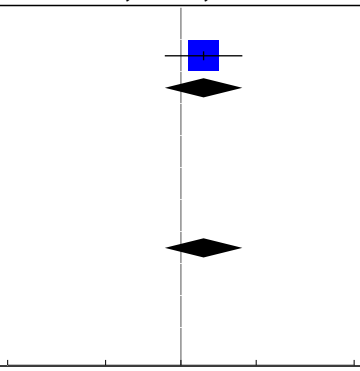
Analysis 1.30. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 30 Infant febrile illness episodes.

		Infant febrile illness episodes		
Study	**Outcome / Details**	**Vitamin A**	**Control**	**Significance**
		200,000 IU versus no treatment		
Roy 1997	Febrile illness episodes (mean episodes per child-week of observation)	0.1 (95% CI 0.09 to 0.11)	0.3 (95% CI 0.27 to 0.30)	P < 0.002
Roy 1997	Child-weeks	515	522	

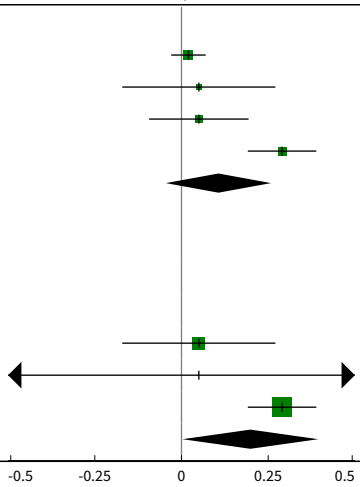
Analysis 1.31. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 31 Infant adverse effects of supplementation.

Study or subgroup	**Supplement n/N**	**Placebo n/N**	**Risk Ratio M-H, Random, 95% CI**	**Weight**	**Risk Ratio M-H, Random, 95% CI**
1.31.1 Bulging fontanelle: 400,000 IU versus placebo					
Ayah 2007	8/222	4/222		100%	2[0.61,6.55]
Subtotal (95% CI)	**222**	**222**		**100%**	**2[0.61,6.55]**
Total events: 8 (Supplement), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					
Total (95% CI)	**222**	**222**		**100%**	**2[0.61,6.55]**
Total events: 8 (Supplement), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					



Analysis 1.32. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 32 Infant serum retinol (mcmol/L) at 3 - 3.5 months postpartum.

Study or subgroup	**Supplement N**	**Supplement Mean(SD)**	**Placebo N**	**Placebo Mean(SD)**	**Mean Difference Random, 95% CI**	**Weight**	**Mean Difference Random, 95% CI**
1.32.1 200,000 - 400,000 IU versus no treatment							
Ayah 2007	78	0.9 (0.2)	86	0.9 (0.1)		29.87%	0.02[-0.03,0.07]
Bhaskaram 2000	49	0.9 (0.6)	40	0.9 (0.5)		18.66%	0.05[-0.17,0.27]
Martins 2010	30	0.7 (0.3)	29	0.6 (0.3)		24.18%	0.05[-0.09,0.19]
Vinutha 2000	38	1.1 (0.2)	29	0.8 (0.2)		27.29%	0.29[0.19,0.39]
Subtotal ***	**195**		**184**			**100%**	**0.11[-0.05,0.26]**
Heterogeneity: Tau^2=0.02; Chi^2=23.04, df=3(P<0.0001); I^2=86.98%							
Test for overall effect: Z=1.38(P=0.17)							
1.32.2 200,000 IU versus placebo or no treatment							
Bhaskaram 2000	49	0.9 (0.6)	40	0.9 (0.5)		38.03%	0.05[-0.17,0.27]
Martins 2010	30	0.7 (26)	29	0.6 (0.3)		0.04%	0.05[-9.25,9.35]
Vinutha 2000	38	1.1 (0.2)	29	0.8 (0.2)		61.93%	0.29[0.19,0.39]
Subtotal ***	**117**		**98**			**100%**	**0.2[0,0.39]**



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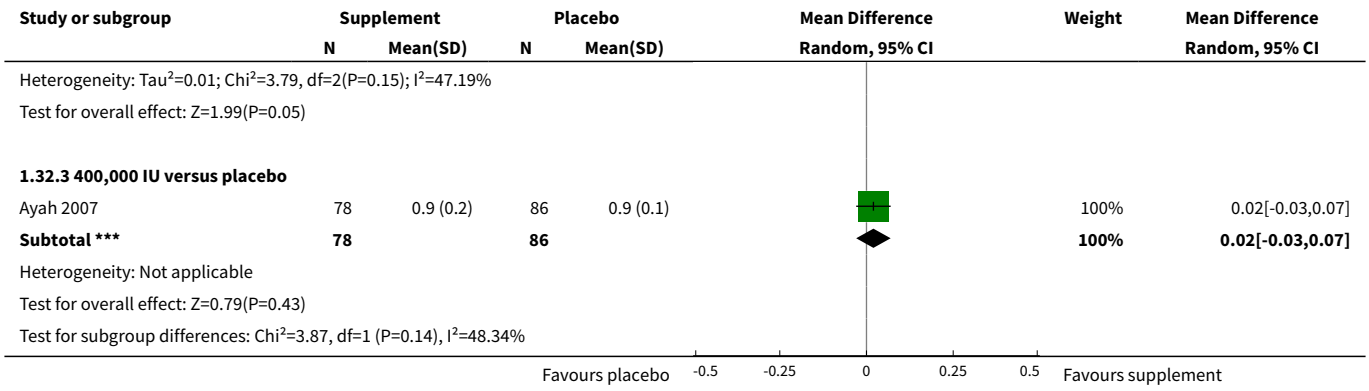
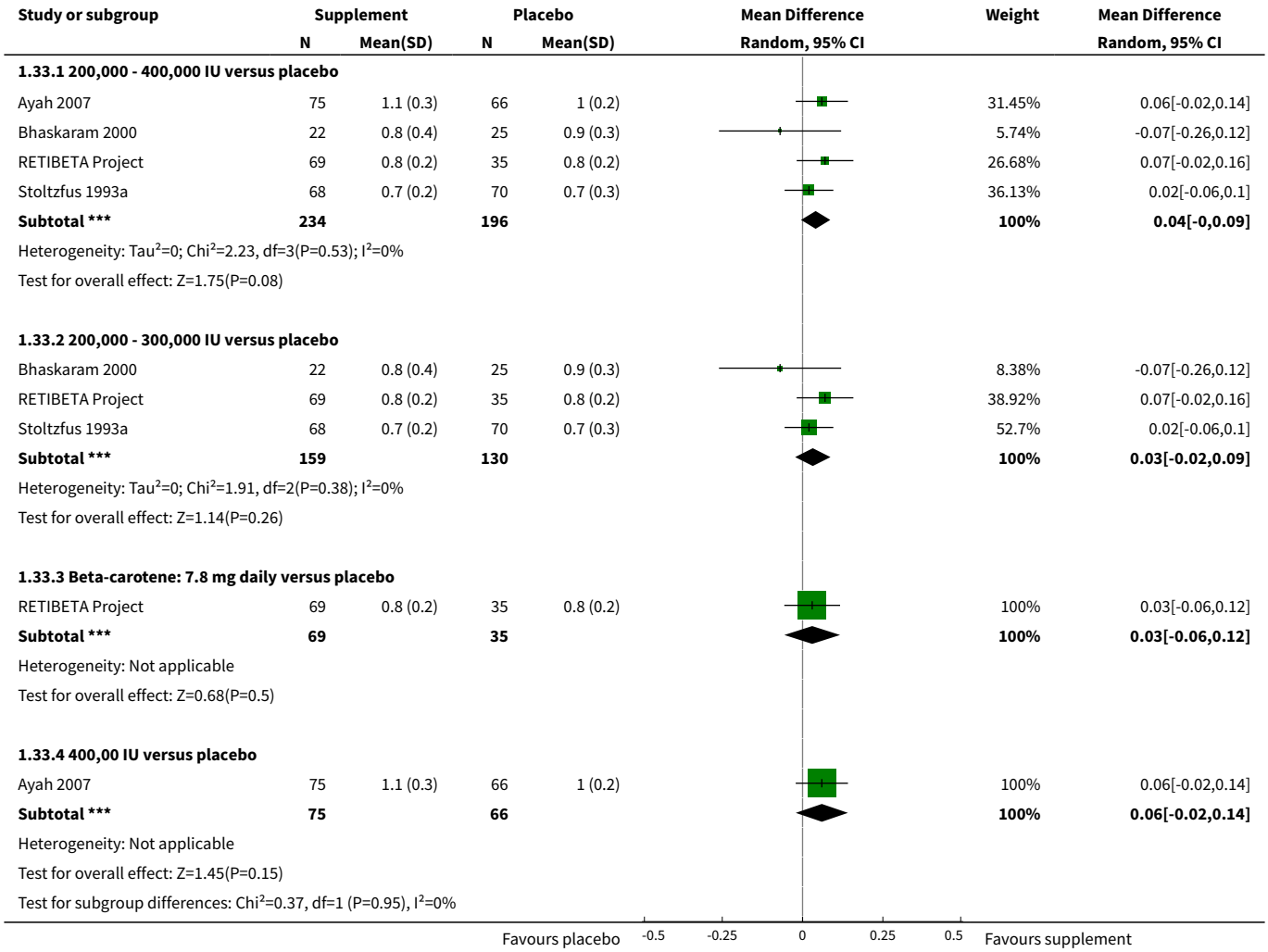


Analysis 1.33. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 33 Infant serum retinol (mcmol/L) at 6 - 6.5 months postpartum.



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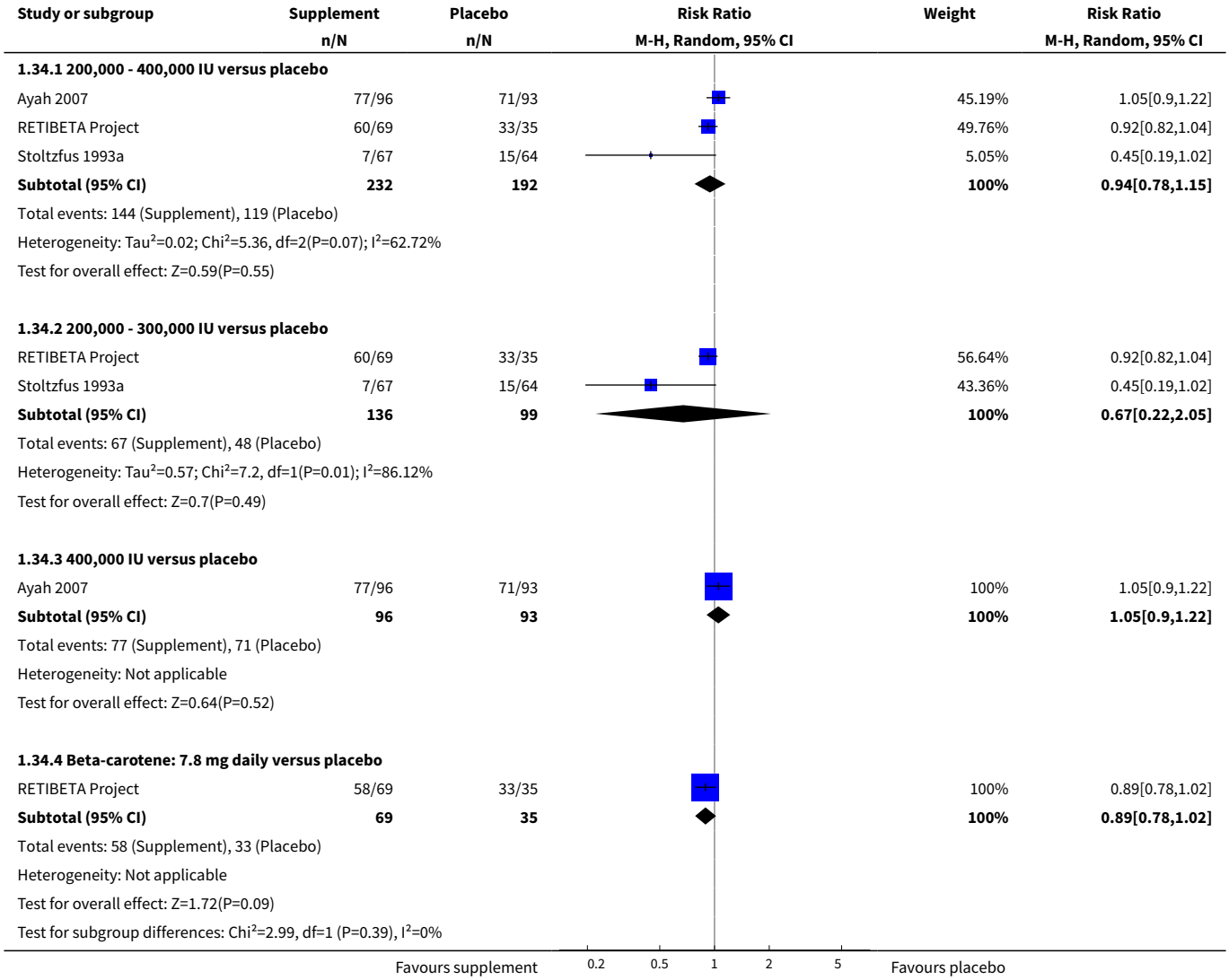
Analysis 1.34. Comparison 1 Supplement (vitamin A as retinyl, water-miscible or beta-carotene) 200,000 to 400,000 IU versus control (placebo, no treatment, other), Outcome 34 Infant low hepatic vitamin A reserves at 6 - 6.5 months postpartum.



Comparison 2. Supplement (vitamin A as retinyl) 400,000 IU versus 200,000 IU

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Maternal serum retinol (mcmol/L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 400,000 IU versus 200,000 IU at 2 months postpartum	2	429	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.06, 0.14]
1.2 400,000 IU versus 200,000 IU at 4 months postpartum	1	213	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.29, 0.05]

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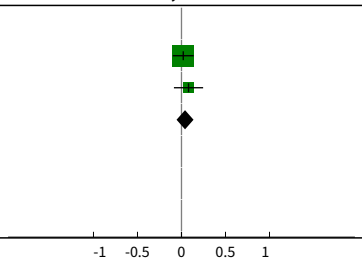
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 400,000 IU versus 200,000 IU at 6 months postpartum	1	200	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.24, 0.08]
2 Maternal breast milk retinol (mcmol/L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 400,000 IU versus 200,000 IU at 2 months postpartum	2	377	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.14, 0.11]
2.2 400,000 IU versus 200,000 IU at 3 months postpartum	1	190	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.28, 0.16]
2.3 400,000 IU versus 200,000 IU at 4 months postpartum	2	348	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.13, 0.08]
2.4 400,000 IU versus 200,000 IU at 6 months postpartum	1	192	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.13, 0.31]
3 Maternal breast milk retinol (< 1.05 mcmol/L)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 400,000 IU versus 200,000 IU at 3 months postpartum	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.72, 2.17]
3.2 400,000 IU versus 200,000 IU at 6 months postpartum	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.53, 1.25]
4 Infant serum retinol (mcmol/L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 400,000 IU versus 200,000 IU at 2 months postpartum	2	362	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.05, 0.07]
4.2 400,000 IU versus 200,000 IU at 4 months postpartum	1	192	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.20, 0.14]
4.3 400,000 IU versus 200,000 IU at 6 months postpartum	1	173	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.23, 0.11]

Analysis 2.1. Comparison 2 Supplement (vitamin A as retinyl) 400,000 IU versus 200,000 IU, Outcome 1 Maternal serum retinol (mcmol/L).

Study or subgroup	High dose N	High dose Mean(SD)	Low dose N	Low dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 400,000 IU versus 200,000 IU at 2 months postpartum							
Darboe 2007	96	1.4 (0.4)	97	1.4 (0.4)		66.15%	0.02[-0.1,0.14]
Fernandes 2012	119	2 (0.7)	117	2 (0.6)		33.85%	0.08[-0.09,0.25]
Subtotal ***	**215**		**214**			**100%**	**0.04[-0.06,0.14]**
Heterogeneity: Tau²=0; Chi²=0.33, df=1(P=0.56); I²=0%							
Test for overall effect: Z=0.82(P=0.41)							



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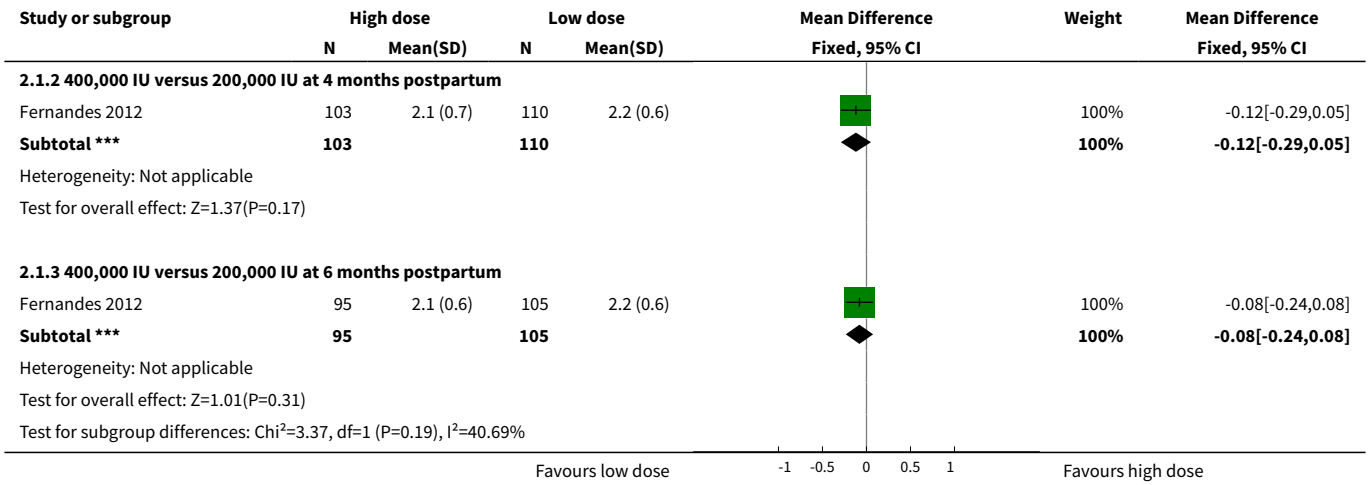
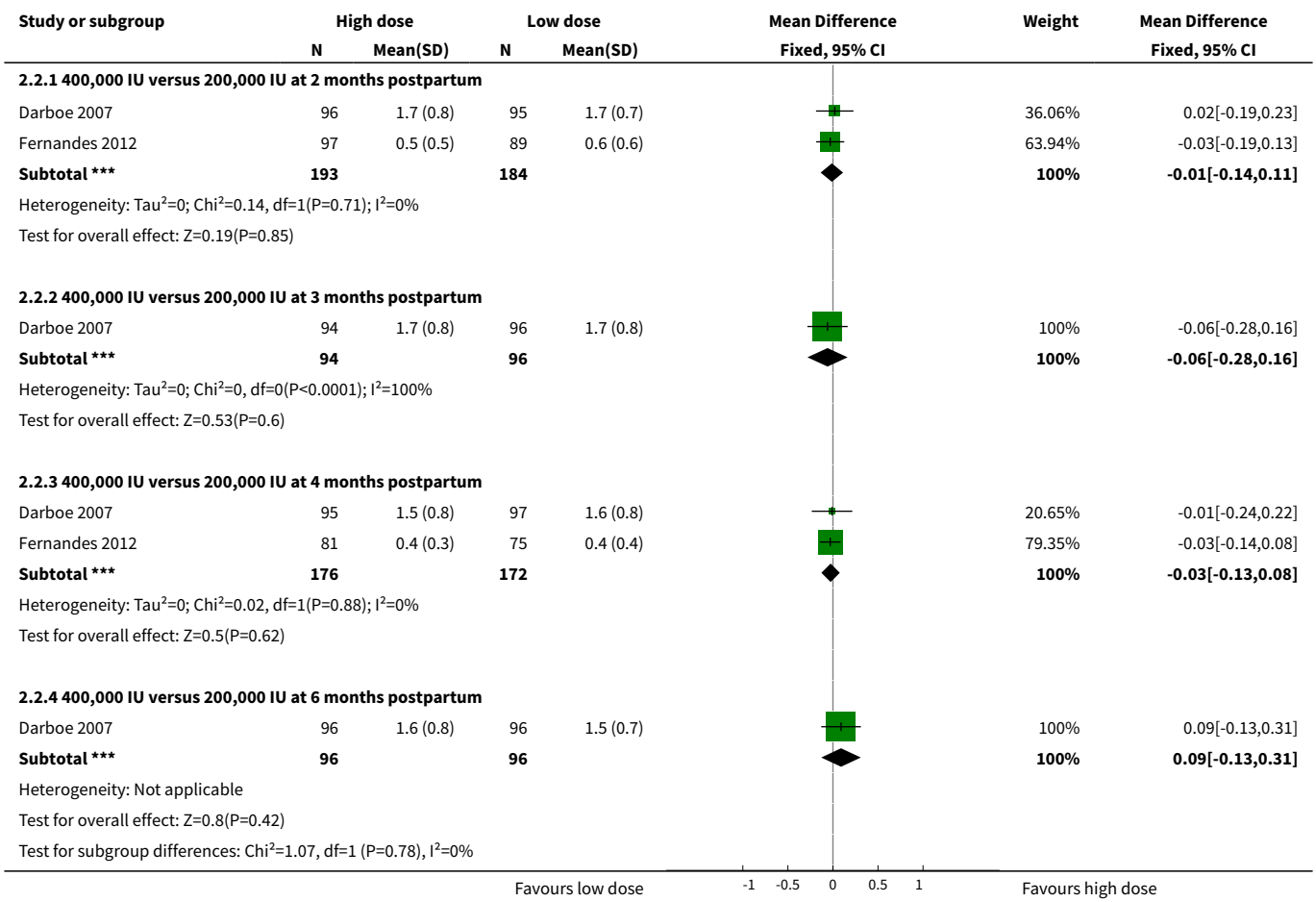


Analysis 2.2. Comparison 2 Supplement (vitamin A as retinyl) 400,000 IU versus 200,000 IU, Outcome 2 Maternal breast milk retinol (mcmol/L).



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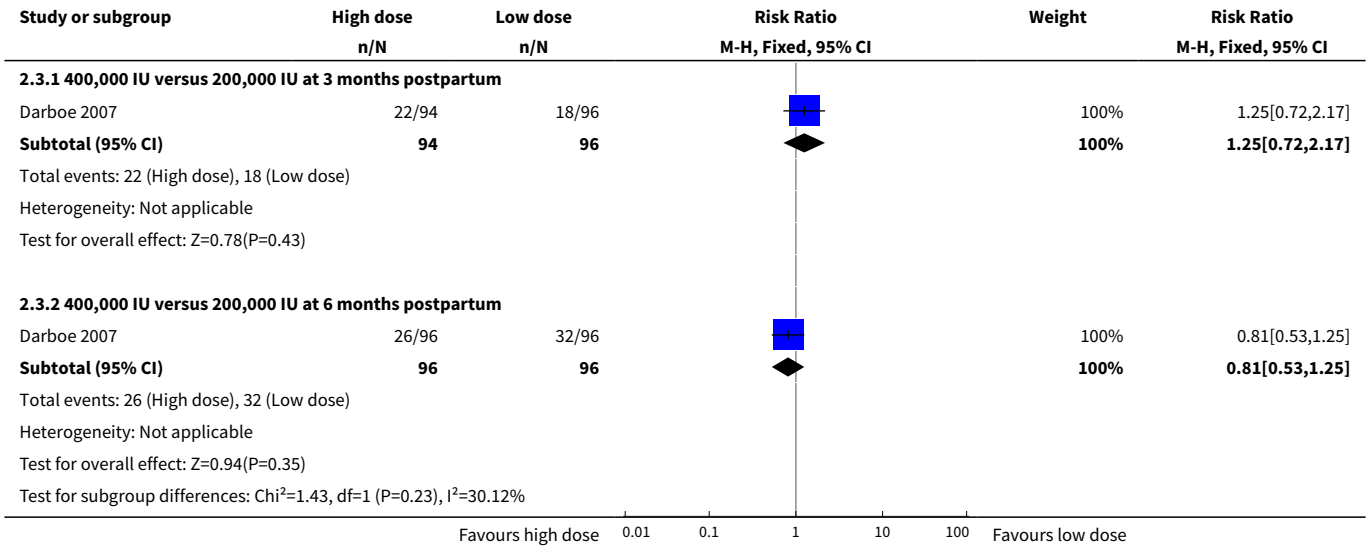
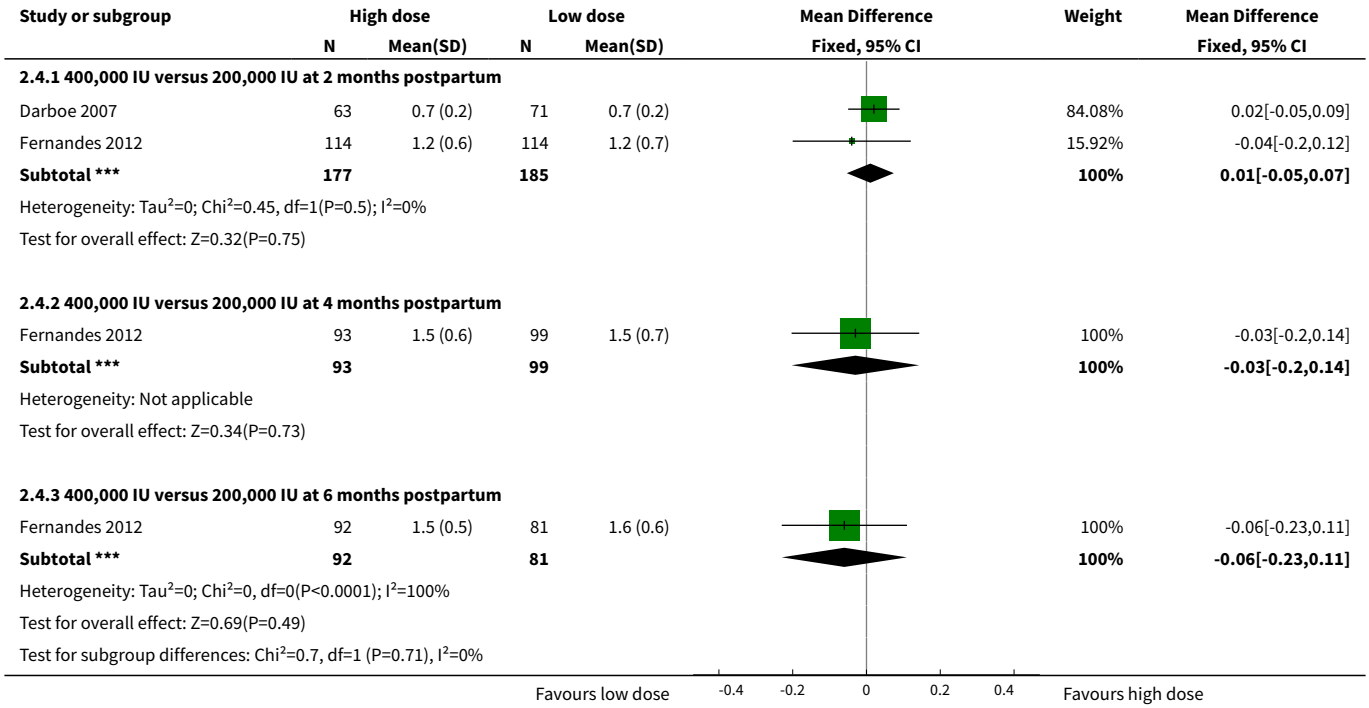
Analysis 2.3. Comparison 2 Supplement (vitamin A as retinyl) 400,000 IU versus 200,000 IU, Outcome 3 Maternal breast milk retinol (< 1.05 mcmol/L).



Analysis 2.4. Comparison 2 Supplement (vitamin A as retinyl) 400,000 IU versus 200,000 IU, Outcome 4 Infant serum retinol (mcmol/L).



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APPENDICES

Appendix 1. Additional search strategies

LILACS - Latin American and Caribbean Health Sciences by Bireme (1982 to December 2015)
#1: ((Pt ENSAIO CONTROLADO ALEATORIO OR Pt ENSAIO CLINICO CONTROLADO OR Mh ENSAIOS CONTROLADOS ALEATORIOS OR Mh DISTRIBUICAO ALEATORIA OR Mh MÉTODO DUPLO-CEGO OR Mh MÉTODO SIMPLES-CEGO) AND NOT (Ct ANIMAIS AND NOT (Ct HUMANO AND Ct ANIMAIS)) OR (Pt ENSAIO CLÍNICO OR Ex E05.318.760.535$) OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh PLACEBOS OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR (Mh PROJETOS DE PESQUISA) AND NOT (Ct ANIMAIS AND NOT (Ct HUMANO AND Ct ANIMAIS)) OR (Ct ESTUDO COMPARATIVO OR Ex E05.337$ OR Mh SEGUIMENTOS OR Mh ESTUDOS PROSPECTIVOS OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct ANIMAIS AND NOT (Ct HUMANO AND Ct ANIMAIS))) AND NOT Mh ANIMAIS [Palavras]
#2: retinol or "vitamin A" or caroten$ [Palavras]
#3: #1 AND #2

WEB OF SCIENCE by ISI (1945 to December 2015)
#1: TS=(randomised controlled trial) OR TS=(controlled clinical trial) OR TS=(randomised controlled trials) OR TS=(random allocation) OR TS=(double-blind method) OR TS=(single-blind method) OR TS=(clinical trial) OR TS=(clinical trials) OR TS=(clinical trial) OR ((TS=singl* OR TS=doubl* OR TS=trebl* OR TS=tripl*) AND (TS=mask* OR TS=blind*)) OR (TS=(latin square) OR TS=placebo* OR TS=random* OR TS=(research design) or TS=(comparative study) OR TS=(evaluation studies) OR TS=(follow-up studies) OR TS=(prospective studies) OR TS=(cross-over studies) OR TS=control* OR TS=prospectiv* OR TS=volunteer*)
#2: TS=puerp* or TS=matern* or TS=lacta* or TS=breastfe* or TS=(breast fee*) or TS=breast-fee* or TS=(human milk) or TS=postnatal or TS=postpart* or TS=newborn* or TS=infant* or TS=newborn
#3: TS=retinol* or TS=(vitamin A) or TS=caroten*
#4: #3 AND #2 AND #1

WHAT'S NEW

Date	Event	Description
28 April 2016	Amended	The text in the results section on selection bias has been corrected.

HISTORY

Protocol first published: Issue 2, 2006
Review first published: Issue 10, 2010

Date	Event	Description
15 February 2016	New citation required but conclusions have not changed	Search updated and two new studies have been included in this review update (Fernandes 2012; Martins 2010).
15 February 2016	New search has been performed	A new search was conducted. The addition of two studies in the 2016 update of this review did not meaningfully change the conclusions of the original review (Oliveira-Menegozzo 2010).
22 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

JM Oliveira, R Allert (new to the authorship for the 2016 update) and CE East updated this review.

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Cochrane Editorial Unit, UK.

  The Cochrane Editorial Unit, Cochrane Central Executive (Toby Lasserson, Newton Opiyo) assisted in the use of GRADE and in the development of the 'Summary of findings' table.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Considerable collaborative input from referees, authors and other Cochrane personnel during preparation of the original review resulted in a focus specifically on postpartum supplementation, rather than widening to include long-term supplementation during women's reproductive years or of infant supplementation (these were covered by separate reviews). At that time, we also added the potential for including cluster-randomised trials, which were considered important for the purpose of the review, although none were ultimately included.

In the 2016 update, we have edited the methods to incorporate changes over time to the methodology of the Pregnancy and Chidlbirth Group. Specifically, and to avoid double counting, we adjusted the numbers of events (dichotomous outcomes) and total numbers (continuous or dichotomous outcomes) contributing to the control group of the RETIBETA Project, as there were two comparisons made with different forms of vitamin A supplementation.

INDEX TERMS

Medical Subject Headings (MeSH)

*Postpartum Period; Infant Mortality; Maternal Mortality; Milk, Human [chemistry]; Randomized Controlled Trials as Topic; Vitamin A [*administration & dosage] [analysis]; Vitamin A Deficiency [drug therapy]; Vitamins [*administration & dosage]

MeSH check words

Female; Humans; Infant; Infant, Newborn; Pregnancy

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