Vitamin E supplementation in pregnancy (Review)

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Vitamin E supplementation in pregnancy

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A B S T R A C T

Background

Vitamin E supplementation may help reduce the risk of pregnancy complications involving oxidative stress, such as pre-eclampsia. There is a need to evaluate the efficacy and safety of vitamin E supplementation in pregnancy.

Objectives

To assess the effects of vitamin E supplementation, alone or in combination with other separate supplements, on pregnancy outcomes, adverse events, side effects and use of health services.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 March 2015) and reference lists of retrieved studies.

Selection criteria

All randomised or quasi-randomised controlled trials evaluating vitamin E supplementation in pregnant women. We excluded interventions using a multivitamin supplement that contained vitamin E.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

Twenty-one trials, involving 22,129 women were eligible for this review. Four trials did not contribute data. All of the remaining 17 trials assessed vitamin E in combination with vitamin C and/or other agents. Overall the risk of bias ranged from low to unclear to high; 10 trials were judged to be at low risk of bias, six trials to be at unclear risk of bias and five trials to be at high risk of bias. No clear difference was found between women supplemented with vitamin E in combination with other supplements during pregnancy compared with placebo for the risk of stillbirth (risk ratio (RR) 1.17, 95% confidence interval (CI) 0.88 to 1.56, nine studies, 19,023 participants, I^2 = 0%; *moderate quality evidence*), neonatal death (RR 0.81, 95% CI 0.58 to 1.13, nine trials, 18,617 participants, I^2 = 0%), pre-eclampsia (average RR 0.91, 95% CI 0.79 to 1.06; 14 trials, 20,878 participants; I^2 = 48%; *moderate quality evidence*), preterm birth (average RR 0.98, 95% CI 0.88 to 1.09, 11 trials, 20,565 participants, I^2 = 52%; *high quality evidence*) or intrauterine growth

restriction (RR 0.98, 95% CI 0.91 to 1.06, 11 trials, 20,202 participants, I² = 17%; *high quality evidence*). Women supplemented with vitamin E in combination with other supplements compared with placebo were at decreased risk of having a placental abruption (RR 0.64, 95% CI 0.44 to 0.93, seven trials, 14,922 participants, I² = 0%; *high quality evidence*). Conversely, supplementation with vitamin E was associated with an increased risk of self-reported abdominal pain (RR 1.66, 95% CI 1.16 to 2.37, one trial, 1877 participants) and term prelabour rupture of membranes (PROM) (average RR 1.77, 95% CI 1.37 to 2.28, two trials, 2504 participants, I² = 0%); however, there was no corresponding increased risk for preterm PROM (average RR 1.27, 95% CI 0.93 to 1.75, five trials, 1999 participants, I² = 66%; *low quality evidence*). There were no clear differences between the vitamin E and placebo or control groups for any other maternal or infant outcomes. There were no clear differing patterns in subgroups of women based on the timing of commencement of supplementation or baseline risk of adverse pregnancy outcomes. The GRADE quality of the evidence was high for preterm birth, intrauterine growth restriction and placental abruption, moderate for stillbirth and clinical pre-eclampsia, and low for preterm PROM.

Authors' conclusions

The data do not support routine vitamin E supplementation in combination with other supplements for the prevention of stillbirth, neonatal death, preterm birth, pre-eclampsia, preterm or term PROM or poor fetal growth. Further research is required to elucidate the possible role of vitamin E in the prevention of placental abruption. There was no convincing evidence that vitamin E supplementation in combination with other supplements results in other important benefits or harms.

P L A I N   L A N G U A G E   S U M M A R Y

Vitamin E supplementation in pregnancy

What is the issue?

Does giving vitamin E supplementation, alone or in combination with other vitamins, given to women during pregnancy improve outcomes for their babies by reducing the incidence of pre-eclampsia and the number of babies born too early? Or does it cause harm?

Why is this important?

Although vitamin E deficiency is rarely seen in healthy adults, for pregnant women, insufficient dietary vitamin E (found in vegetable oils, nuts, cereals and some leafy green vegetables) may lead to complications such as pre-eclampsia and the baby being born small. In addition, vitamin E deficiency can be made worse by too much iron and so it is important to investigate the optimum amounts for pregnancy.

What evidence did we find?

This review included 21 trials involving over 21,000 women. Four trials did not contribute data to the analyses. The trials were generally of variable quality. There were just three studies on vitamin E supplementation alone, but none of these studies contributed data. All other studies included vitamin C, and additional supplements or drugs.

The findings indicate that routine supplementation with vitamin E in combination with other supplements during pregnancy did not improve outcomes for babies or women. There was a reduction in the number of placentas coming away early (placental abruption) in women given vitamin E supplements in combination with other agents, which was rated as high-quality evidence. However, it is unclear whether this finding was due to vitamin E or the other agents used in the supplement. This should be explored in further research examining the mechanisms leading to placental abruption.

The review found there may be harms associated with vitamin E supplements in pregnancy, as there was an increased risk of abdominal pain and term prelabour rupture of fetal membranes in women supplemented with vitamin E in combination with other supplements. There was no increase in preterm prelabour rupture of membranes in women supplemented with vitamin E and other agents.

What does this mean?

The large body of evidence does not support taking vitamin E supplements, alone or in combination, during pregnancy. This is because taking vitamin E in combination with other supplements during pregnancy does not help to prevent problems in pregnancy including stillbirth, baby death, preterm birth, pre-eclampsia or low birthweight babies. In fact, it may increase abdominal pain for women and also increase the number of women having early rupture of membranes at term.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Any vitamin E supplementation versus placebo, no placebo or other supplements

Population: pregnant women receiving vitamin E supplementation or control, living in areas where there is either inadequate dietary intake of vitamin E or where there is presumed adequate intake.
Settings: Australia, Brazil, Canada, Holland, India, Iran, Malaysia, Mexico, Peru, South Africa, Turkey, UK, USA, Vietnam, Venezuela.
Intervention: any vitamin E supplementation versus placebo, no placebo or other supplements

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE) Comments
	Assumed risk	**Corresponding risk**			
	Control	**Any vitamin E supple-mentation**			
Stillbirth	**Study population**		**RR 1.17** (0.88 to 1.56)	19023 (9 studies)	⊕⊕⊕◯ **moderate**[1]
	9 per 1000	**11 per 1000** (8 to 14)			
	Moderate				
	14 per 1000	**16 per 1000** (12 to 22)			
Preterm birth (less than 37 weeks' gesta-tion)	**Study population**		**RR 0.98** (0.88 to 1.09)	20565 (11 studies)	⊕⊕⊕⊕ **high**
	159 per 1000	**156 per 1000** (140 to 173)			
	Moderate				
	235 per 1000	**230 per 1000** (207 to 256)			

Clinical pre-eclampsia (random-effects model)	Study population		RR 0.91 (0.79 to 1.06)	20878 (14 studies)	⊕⊕⊕◯ moderate[3]
	95 per 1000	87 per 1000 (75 to 101)			
	Moderate				
	146 per 1000	133 per 1000 (115 to 155)			
Intrauterine growth restriction (various definitions)	Study population		RR 0.98 (0.91 to 1.06)	20202 (11 studies)	⊕⊕⊕⊕ high
	106 per 1000	104 per 1000 (97 to 113)			
	Moderate				
	119 per 1000	117 per 1000 (108 to 126)			
Prelabour rupture of fetal membranes - preterm	Study population		RR 1.27 (0.93 to 1.75)	1999 (5 studies)	⊕⊕◯◯ low[1,2]
	29 per 1000	37 per 1000 (25 to 55)			
	Moderate				
	26 per 1000	33 per 1000 (22 to 50)			
Bleeding episodes (placental abruption)	Study population		RR 0.64 (0.44 to 0.93)	14922 (7 studies)	⊕⊕⊕⊕ high
	9 per 1000	6 per 1000 (4 to 9)			
	Moderate				

19 per 1000	12 per 1000 (8 to 18)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Wide confidence interval crossing the line of no effect.

[2] Statistical Heterogeneity (I² > 60%).

[3] Publication bias detected.

BACKGROUND

Description of the condition

Vitamin E is the generic name given to eight lipid-soluble and plant-derived compounds; four are referred to as tocopherols (alpha, beta, gamma, delta) and four are known as tocotrienols (alpha, beta, gamma, delta) (Roberts 1990). Natural source alpha-tocopherol is the most biologically active form of vitamin E, and consequently vitamin E activity is expressed in terms of alpha-tocopherol equivalents (mg alpha-TE). In foods, the main source of tocopherol is wheatgerm oil and other vegetable oils, nuts, in the fat of meat, some cereals and some leafy green vegetables (NHMRC 2006). Synthetic forms of vitamin E are also available and commonly used in vitamin preparations; however, these forms have less biological activity than their naturally occurring counterparts (IOM 2000).

Vitamin E deficiency is rarely seen in healthy adults and has primarily been characterised in preterm infants, low birthweight infants and those with fat malabsorption disorders. Reported symptoms of deficiency include haemolytic anaemia, reticulocytosis, hyperbilirubinaemia, low haemoglobin levels (Gross 1982) and peripheral neuropathy (Roberts 1990). Vitamin E deficiency is exacerbated in the presence of iron overload and a high dietary intake of polyunsaturated fatty acids (PUFAs), which is of particular relevance for preterm infants fed formula containing high levels of iron and PUFAs (Roberts 1990). Establishing a recommended dietary intake (RDI) of vitamin E has been impeded by the low observance of overt vitamin E deficiency; however, current RDI range from 7 mg to 10 mg alpha-TE (Roberts 1990). During pregnancy, losses of vitamin E to the fetus are thought to be minimal and thus the RDI during pregnancy is often unchanged (NHMRC 2006).

Description of the intervention

Vitamin E functions as an antioxidant in the lipid phase, protecting phospholipid fatty acids from oxidation by harmful free radicals (reactive oxygen molecules) and thus stabilising cell membranes. As an antioxidant, vitamin E helps to prevent oxidative stress, which is characterised by an excess of free radicals coupled with decreased antioxidants available to quench these free radicals. Vitamin E interacts synergistically with vitamin C, a water soluble antioxidant, where vitamin C helps to convert oxidised vitamin E back into a useful form (Packer 1979). This relationship may account for the limited observation of overt vitamin E deficiency in humans, as vitamin C may aid in recycling vitamin E stores. Vitamin E and vitamin C supplements are often given concurrently to utilise this relationship and to promote antioxidant defences in both the aqueous and lipid phase. Little is known about other potential functions of vitamin E as research to date has focused on

its antioxidant properties. Doses of vitamin E required to have an antioxidant effect have been reported at least to 400 international units (approximately 268 mg alpha-TE) (Devaraj 1997).

How the intervention might work

Oxidative stress has been linked to the development of adult diseases including cardiovascular disease, cancer, chronic inflammation and neurologic disorders, resulting in many large multicentre clinical trials of vitamin E supplementation. However, the results of these large trials of vitamin E supplementation have been disappointing and in fact provide evidence of harm, including an increased risk of mortality (Bjelakovic 2012; Bjelakovic 2013). During pregnancy, oxidative stress has been implicated in the development of pre-eclampsia (Roberts 1990), and proposed in the disease processes of intrauterine growth restriction (Kingdom 2000) and prelabour rupture of membranes(PROM) both preterm and at term (Woods 2001). Oxidative stress has also been implicated in many of the disorders common to preterm infants including chronic lung disease, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, necrotising enterocolitis and bronchopulmonary dysplasia (Saugstad 1988; Saugstad 2001). Preventing complications in pregnancy like pre-eclampsia, growth restriction, preterm PROM and serious neonatal morbidities would represent significant cost savings in hospital and intensive care unit admissions and the use of other healthcare resources. Other Cochrane reviews are assessing 'Antioxidants for preventing pre-eclampsia' (Rumbold 2005a) and 'Vitamin C supplementation in pregnancy' (Rumbold 2005b).

Why it is important to do this review

Vitamin E appears to have low toxicity in humans. However there is limited evidence on the safety of using vitamin E in pregnancy. Despite the lack of evidence on safety, the United States Institute of Medicine Food and Nutrition Board has set an upper tolerable limit of vitamin E ingestion in pregnancy at 1000 mg per day (IOM 2000), indicating the highest level of intake that is likely to pose no risk of adverse health effects to almost all women. In non-pregnant adults controlled clinical trials of vitamin E supplementation in a variety of doses have failed to demonstrate any consistent side effects (Bendich 1993). Observational studies, however, have reported adverse effects including fatigue, weakness, creatinuria, dermatitis, reduced thyroid function, increased urinary androgen excretion, reduced leukocyte action and altered coagulation factors resulting in increased bleeding in vitamin K deficient individuals (Bendich 1993; Roberts 1990). The mechanisms leading to altered coagulation factors are unclear; however, vitamin E has been reported to potentiate the effect of anticoagulant therapy, such as warfarin. Newborn infants have a relative vitamin K deficiency at birth, hence vitamin E supplementation during

pregnancy may influence the risk of vitamin K deficiency bleeding or haemorrhagic disease of the newborn unfavourably if vitamin K is not given at birth. In controlled trials of vitamin E supplementation in preterm infants for the treatment of retinopathy of prematurity, vitamin E supplementation has been associated with an increased risk of bacterial sepsis and necrotising enterocolitis (Johnson 1985). Given the lipid soluble nature of vitamin E, supplementation may result in increased storage of the vitamin in organs such as the liver, muscle and adipose tissue when used in high doses. The need to demonstrate the efficacy and safety of using vitamin E in pregnancy is particularly important when vitamin E is given in high doses.

The aims of this review are (i) to identify all published, unpublished randomised and quasi-randomised controlled trials investigating vitamin E supplementation in pregnancy and (ii) to investigate the benefits and hazards of vitamin E supplementation in pregnancy.

O B J E C T I V E S

To assess, using the best available evidence, the effects of vitamin E supplementation, alone or in combination with other separate supplements, on pregnancy outcomes, adverse events, side effects and use of health services.

M E T H O D S

Criteria for considering studies for this review

Types of studies

All randomised or quasi-randomised controlled trials evaluating the effect of vitamin E supplementation in pregnant women.

Types of participants

Pregnant women receiving vitamin E supplementation or control, living in areas where there is either inadequate dietary intake of vitamin E or where there is presumed adequate intake.

Women were classified into subgroups where possible, based on:

(a) the dosage of the vitamin E supplement (above or equal to/ below the recommended dietary intake of 7 mg alpha-TE);

(b) the gestation at trial entry (trial entry less than 20 weeks or greater than or equal to 20 weeks);

(c) whether women have low or adequate dietary vitamin E intake prior to trial entry (low intake defined as intake less than the recommended dietary intake in that setting as measured by dietary questionnaire);

(d) the use of vitamin E in combination with other dietary supplements;

(e) women's risk status for adverse pregnancy outcomes (as defined by the trial authors).

Types of interventions

Vitamin E supplementation, alone or in combination with other separate supplements compared with placebo, no placebo or other supplements. Interventions using a multivitamin supplement (more than two vitamins or minerals combined in the one tablet preparation) that contained vitamin E were excluded.

Types of outcome measures

Primary outcomes

Maternal

1. Development of clinical pre-eclampsia
2. Maternal haematological measures: haemolytic anaemia, reticulocytosis, hyperbilirubinaemia and haemoglobin concentrations
3. Preterm birth (defined as less than 37 weeks' gestation)

Neonatal

1. Stillbirth, neonatal death, perinatal death
2. Infant haematological measures: haemolytic anaemia, reticulocytosis, hyperbilirubinaemia and haemoglobin concentrations
3. Intrauterine growth restriction (defined as birthweight less than third centile or the most extreme centile reported)

Secondary outcomes

Maternal

1. Prelabour rupture of membranes (PROM), preterm and at term
2. Death up to six weeks postpartum
3. Elective delivery (induction of labour or elective caesarean section)
4. Caesarean section (emergency plus elective)
5. Bleeding episodes (such as placental abruption, antepartum hemorrhage, postpartum hemorrhage, complications of epidural anaesthesia, need for transfusion)
6. Measures of serious maternal morbidity (such as eclampsia, liver failure, renal failure, disseminated intravascular coagulation, pulmonary oedema), peripheral neuropathy
7. Adverse events related to vitamin E supplementation sufficient to stop supplementation

8. Side effects of vitamin E supplementation such as fatigue, weakness, altered coagulation times, immunosuppression, creatinuria, dermatitis, altered thyroid function and increased urinary androgen excretion

9. Maternal satisfaction with care

Neonatal

1. Birthweight
2. Infant death
3. Gestational age at birth
4. Congenital malformations
5. Apgar score less than seven at five minutes
6. Vitamin K deficiency bleeding or haemorrhagic disease of the newborn
7. Respiratory distress syndrome
8. Chronic lung disease or bronchopulmonary dysplasia
9. Periventricular hemorrhage
10. Periventricular leukomalacia
11. Bacterial sepsis
12. Necrotising enterocolitis
13. Retinopathy of prematurity
14. Peripheral neuropathy
15. Disability at childhood follow-up (such as cerebral palsy, intellectual disability, hearing disability and visual impairment)
16. Poor childhood growth

Use of health service resources

Woman

1. Antenatal hospital admission
2. Visits to day care units
3. Use of intensive care
4. Ventilation
5. Dialysis

Infant

1. Admission to special care/intensive care nursery
2. Duration of mechanical ventilation
3. Length of stay in hospital
4. Development
5. Special needs after discharge

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 (31 March 2015).

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.

Details of the 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 can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

[See Appendix 1 for details of additional searches carried out in the previous version of the review (Rumbold 2005).]

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* Rumbold 2005.

For this update, the following methods were used for assessing the 62 reports that were identified as a result of the updated search. 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 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.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.

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

Assessment of risk of bias in included studies

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

(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);
- 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 also explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of quality of the evidence

For this update, we assessed the quality of the evidence using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons:

1. stillbirth;
2. preterm birth (defined as less than 37 weeks' gestation);
3. development of clinical pre-eclampsia;
4. intrauterine growth restriction (defined as birthweight less than third centile or the most extreme centile reported);
5. preterm prelabour rupture of membranes (PROM) ;
6. bleeding episodes (placental abruption).

We used the GRADE profiler (GRADE 2014) 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 did not identify any cluster-randomised trials in this update. In future updates, we will include cluster-randomised trials in the analyses along with individually-randomised trials,we will adjust their sample sizes using the methods described in the *Handbook* 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 trial

This is not a valid study design for this review.

Other unit of analysis issues

In future updates, if we include multi-arm studies (more than one treatment group), we will combine treatment groups if appropriate, and create a single pair-wise comparison. We will not double count participants according to methods described in the *Handbook* (Higgins 2011).

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, 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, we carried out analyses, 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 Tau², I² and Chi² statistics. We regarded heterogeneity as substantial if an I² was greater than 30% and either a Tau² was greater than zero, or there was a low P value (less than 0.10) in the Chi² test for heterogeneity. If we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis we investigated reporting biases (such as publication bias) using funnel plots for primary outcomes. We assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we explored possible reasons.

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 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 did not combine trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau² and I².

Subgroup analysis and investigation of heterogeneity

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

We carried out the following subgroup analyses for primary outcomes:

1. the dosage of the vitamin E supplement (above or equal to versus below the recommended dietary intake of 7 mg alpha-TE);
2. the gestation at trial entry (trial entry less than 20 weeks versus greater than or equal to 20 weeks);
3. whether women had low versus adequate dietary vitamin E intake prior to trial entry (low intake defined as intake less than

the recommended dietary intake in that setting as measured by dietary questionnaire);
4. the use of vitamin E in combination with other dietary supplements versus vitamin E alone;
5. women's risk status for adverse pregnancy outcomes (as defined by the trial authors) versus all women.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I² value.

Sensitivity analysis

We carried out sensitivity analyses to explore the effect of trial quality assessed by determining the overall risk of bias taking into consideration the method of random sequence generation and allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential bias. Studies with an overall high or unclear risk of bias were excluded from the analyses in order to assess whether this makes any difference to the overall result.

R E S U L T S

Description of studies

Results of the search

We examined 62 reports of 27 trials. In this update, we included 21 trials (Anthony 1996; Beazley 2005; Borna 2005; Chappell 1999; Gulmezoglu 1997; Gungorduk 2014; Huria 2010; Kalpdev 2011; Mahdy 2004; McCance 2010; Nasrolahi 2006; Poston 2006; Pressman 2003; Rivas 2000; Roberts 2010; Rumbold 2006; Sawhney 2000; Shahraki 2006; Spinnato 2007; Villar 2009; Xu 2010), excluded five trials (Bolisetty 2002; Clark 2012; Lietz 2001; Moldenhauer 2002; Wibowo 2012) and one study (Tan 1997) is still awaiting classification because the full paper cannot be traced.

Included studies

We identified 21 trials involving 22,129 women as eligible for inclusion in the review. Of these, 14 trials assessed vitamin E supplementation for the prevention of pre-eclampsia (Beazley 2005; Chappell 1999; Huria 2010; Kalpdev 2011; Mahdy 2004; McCance 2010; Nasrolahi 2006; Poston 2006; Rivas 2000; Roberts 2010; Rumbold 2006; Spinnato 2007; Villar 2009; Xu 2010). Three trials assessed vitamin E supplementation for the prevention of perinatal complications in women with established pre-eclampsia (Anthony 1996; Gulmezoglu 1997; Sawhney 2000).

Two trials assessed whether vitamin E supplementation prolonged the time to birth for women with preterm prelabour rupture of membranes (PROM) (Borna 2005; Gungorduk 2014). One trial assessed vitamin E for the treatment of leg cramps (Shahraki 2006), and one trial assessed the effect of vitamin E supplementation on concentrations of vitamin E in maternal plasma and amniotic fluid (Pressman 2003). Four studies did not report any clinically meaningful outcomes (Anthony 1996; Pressman 2003; Sawhney 2000; Shahraki 2006), therefore in the meta-analyses data were analysed for 17 studies involving 21,856 women.

Participants

Nine trials recruited women who were at "high" or "increased" risk of pre-eclampsia (Beazley 2005; Chappell 1999; Kalpdev 2011; McCance 2010; Poston 2006; Rivas 2000; Spinnato 2007; Villar 2009; Xu 2010). The criteria for women being at high risk varied between trials, and included: essential hypertension (Kalpdev 2011); type 1 diabetes (McCance 2010); chronic hypertension or a prior history of pre-eclampsia in the most recent pregnancy (Spinnato 2007); previous pre-eclampsia, chronic hypertension, insulin-requiring diabetes mellitus or multiple gestation (Beazley 2005; Xu 2010); abnormal doppler waveform in either uterine artery at 18 to 22 weeks' gestation or a history in the preceding pregnancy of pre-eclampsia necessitating delivery before 37 weeks' gestation, eclampsia or the syndrome of haemolysis, elevated liver enzymes, low platelets (HELLP) (Chappell 1999); chronic hypertension, renal disease, pre-eclampsia-eclampsia in the pregnancy preceding the index pregnancy requiring delivery before 37 weeks' gestation, HELLP syndrome in any previous pregnancy, pregestational diabetes, primiparous with a body mass index (BMI) of ≥ 30 kg/m2, history of medically indicated preterm delivery, abnormal uterine artery Doppler waveforms and women with antiphospholipid syndrome (Villar 2009); pre-eclampsia in the pregnancy preceding the index pregnancy, requiring delivery before 37 weeks' gestation, diagnosis of HELLP in any previous pregnancy, eclampsia in any previous pregnancy, essential hypertension requiring medication, maternal diastolic blood pressure of 90 mm Hg or more before 20 weeks' gestation in the current pregnancy, type 1 or type 2 diabetes, requiring insulin or oral hypoglycaemic therapy, antiphospholipid syndrome, chronic renal disease, multiple pregnancy, abnormal uterine artery doppler waveforms, and primiparity with BMI at first antenatal appointment of ≥ 30 kg/m² (Poston 2006); or nulliparity, previous pre-eclampsia, obesity, hypertension, less than 20 years old, diabetes, nephropathy, mean arterial pressure above of 85 mmHg, positive roll-over test, black race, family history of hypertension or pre-eclampsia, twin pregnancy and poor socioeconomic conditions (Rivas 2000). The trial by Xu 2010 had an additional low-risk arm which included nulliparous women, a further five trials involved women who were either primigravid or nulliparous (Huria 2010; Mahdy 2004; Nasrolahi 2006; Roberts 2010; Rumbold 2006). Three trials included women with established pre-eclamp-

sia (Anthony 1996; Gulmezoglu 1997; Sawhney 2000). Two trials involved women with established preterm PROM(Borna 2005; Gungorduk 2014), and one trial enrolled with pregnant women experiencing leg cramps (Shahraki 2006). The remaining trial involved women with planned caesarean section over 35 weeks of gestation (Pressman 2003).

The timing of commencement of supplementation differed widely, however, most started supplementation in the second trimester. The range in gestational ages at commencement included: eight to 22 weeks' (McCance 2010), nine to 16 weeks' (Roberts 2010), 12 weeks' (Huria 2010), 12 to 18 weeks' (Xu 2010), 12 to 19 weeks' (Spinnato 2007), 13 to 19 weeks' (Kalpdev 2011), 14 to 20 weeks' (Beazley 2005), 14 to 21 weeks' (Poston 2006), 14 to 22 weeks' (Rumbold 2006; Villar 2009), 16 to 22 weeks' (Chappell 1999), 24 to 32 weeks' (Gulmezoglu 1997), 24 to 34 weeks' (Gungorduk 2014), 24 to 34 weeks' (Borna 2005), 25 to 28 weeks' (Shahraki 2006), less than 29 weeks' (Rivas 2000) and 35 weeks' or more (Pressman 2003). For four trials, the commencement of supplementation was unknown (Anthony 1996; Mahdy 2004; Nasrolahi 2006; Sawhney 2000).

Interventions

Three trials supplemented women with vitamin E alone (Anthony 1996; Sawhney 2000; Shahraki 2006). Seventeen trials gave women supplements with vitamin E in addition to vitamin C (Beazley 2005; Borna 2005; Chappell 1999; Gulmezoglu 1997; Gungorduk 2014; Huria 2010; Kalpdev 2011; McCance 2010; Nasrolahi 2006; Poston 2006; Pressman 2003; Rivas 2000; Roberts 2010; Rumbold 2006; Spinnato 2007; Villar 2009; Xu 2010). Of these, two trials supplemented women with additional supplements to vitamin E and vitamin C, either allopurinol (Gulmezoglu 1997) or aspirin and fish oil (Rivas 2000). A further trial supplemented women with a vitamin E rich fraction of palm oil, however no further information was provided (Mahdy 2004). Fifteen trials used the same dose of daily 400 international units (IU) vitamin E (Beazley 2005; Borna 2005; Chappell 1999; Gungorduk 2014; Kalpdev 2011; McCance 2010; Nasrolahi 2006; Poston 2006; Pressman 2003; Rivas 2000; Roberts 2010; Rumbold 2006; Spinnato 2007; Villar 2009; Xu 2010). Three trials gave women either daily 100 mg (Shahraki 2006), 200 IU (Huria 2010) or 800 IU vitamin E (Gulmezoglu 1997). The dose of vitamin E was unknown for three trials (Anthony 1996; Mahdy 2004; Sawhney 2000).

Outcomes

For maternal primary outcomes, development of clinical pre-eclampsia was reported in 14 trials, preterm births was reported in 11 trials, bleeding episodes was reported in seven trials. For neonatal primary outcomes, stillbirth was reported in nine trials, neonatal deaths for nine trials, perinatal deaths for six trials and

intrauterine growth restriction for 11 trials. For secondary outcomes, birthweight was reported in 10 trials, PROM was reported in five trials and maternal death was reported in seven trials.

Settings

The 21 trials were from 15 countries including low- to high-income countries such as Australia, Brazil, Canada, Holland, India, Iran, Malaysia, Mexico, Peru, South Africa, Turkey, UK, USA, Vietnam, and Venezuela. One trial was undertaken in populations with 'evidence of overall low nutritional status' (Villar 2009).

Excluded studies

Five studies were excluded (see Characteristics of excluded studies). Three studies were excluded because they were non-randomised (Bolisetty 2002; Lietz 2001; Moldenhauer 2002). One study was excluded due to intervention was not supplementation but dietary advice to optimise vitamin E intake (Clark 2012). The other study was excluded because the intervention included more than 14 different vitamins (Wibowo 2012).

Risk of bias in included studies

Overall, we judged 10 trials to be at low risk of bias, six trials to be at unclear risk of bias and five trials to be at high risk of bias (Figure 1; Figure 2).

Figure 1.   'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
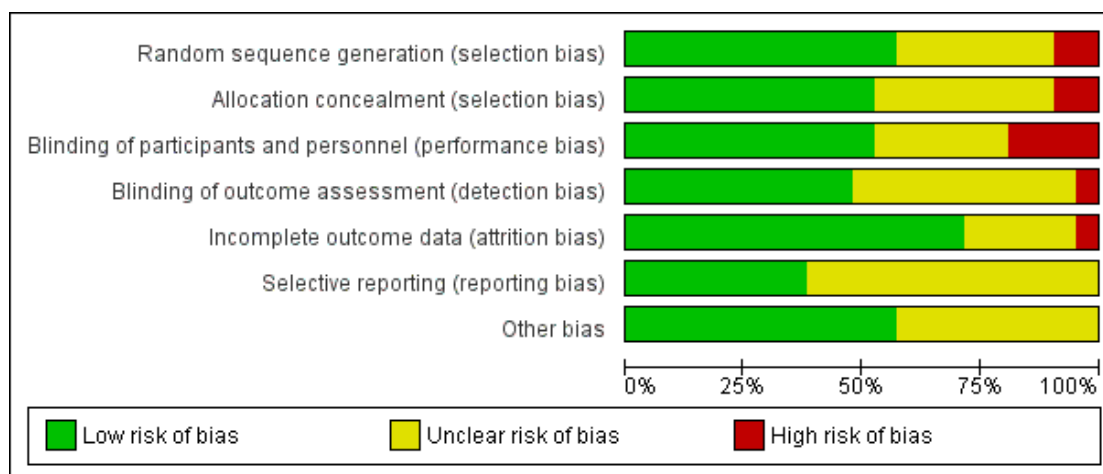
Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Eleven trials were judged to have used adequate methods to generate their random sequence and to conceal allocation (Chappell 1999; Gulmezoglu 1997; Gungorduk 2014; McCance 2010; Poston 2006; Pressman 2003; Roberts 2010; Rumbold 2006; Spinnato 2007; Villar 2009; Xu 2010), and therefore judged to be at low risk of selection bias. One trial (Kalpdev 2011) used adequate methods for sequence generation but provided insufficient detail about allocation concealment and was judged to be at unclear risk of selection bias. Two trials (Nasrolahi 2006; Shahraki 2006) had inadequate methods of both sequence generation and allocation concealment, and were judged to be at high risk of selection bias. The remaining seven trials (Anthony 1996; Beazley 2005; Borna 2005; Huria 2010; Mahdy 2004; Rivas 2000; Sawhney 2000) were judged to be at unclear risk of selection bias as there was insufficient information reported about their methods to permit a judgement.

Blinding

Ten trials undertook adequate blinding of participants, caregivers and outcome assessors and were therefore judged to be at low risk of both performance bias and detection bias (Chappell 1999; Gulmezoglu 1997; McCance 2010; Poston 2006; Pressman 2003; Roberts 2010; Rumbold 2006; Spinnato 2007; Villar 2009; Xu 2010). One study (Borna 2005) had adequate blinding of participants but provided no detail on blinding of outcome assessors, and was therefore judged as having an unclear risk of detection bias. Three trials used no placebo control and were judged to be at high risk of performance bias (Kalpdev 2011; Nasrolahi 2006; Shahraki 2006). Another trial (Gungorduk 2014) used a placebo control, however the tablet was not identical to the vitamin supplement which led to a lack of blinding; this trial was judged to be at high risk of performance and detection bias. Six trials were judged as having an unclear risk of both performance and detection bias due to insufficient information about any methods of blinding (Anthony 1996; Beazley 2005; Huria 2010; Mahdy 2004; Rivas 2000; Sawhney 2000). Four trials were judged as having an unclear risk of detection bias due to lack of information about blinding of outcome assessment (Borna 2005; Kalpdev 2011; Nasrolahi 2006; Shahraki 2006).

Incomplete outcome data

Sixteen trials reported information on attrition and exclusion of participants. Fifteen were judged to have a low risk of attrition bias (Beazley 2005; Chappell 1999; Gulmezoglu 1997; Gungorduk 2014; Kalpdev 2011; McCance 2010; Nasrolahi 2006; Poston 2006; Pressman 2003; Roberts 2010; Rumbold 2006; Shahraki 2006; Spinnato 2007; Villar 2009; Xu 2010), and one was judged to be at high risk (Huria 2010). Five trials provided insufficient information to assess the risk of attrition bias (Anthony 1996; Borna 2005; Mahdy 2004; Rivas 2000; Sawhney 2000).

Selective reporting

Eight trials were judged to be at low risk of reporting bias as they reported data for all expected outcomes (Gungorduk 2014; McCance 2010; Poston 2006; Roberts 2010; Rumbold 2006; Spinnato 2007; Villar 2009; Xu 2010). Thirteen trials were judged to be at unclear risk as there was insufficient information to assess selective reporting (Anthony 1996; Beazley 2005; Borna 2005; Chappell 1999; Gulmezoglu 1997; Huria 2010; Kalpdev 2011; Mahdy 2004; Nasrolahi 2006; Pressman 2003; Rivas 2000; Sawhney 2000; Shahraki 2006).

Other potential sources of bias

Twelve trials were judged to be at low risk of other potential sources of bias (Borna 2005; Chappell 1999; Gulmezoglu 1997; Gungorduk 2014; Kalpdev 2011; McCance 2010; Poston 2006; Pressman 2003; Roberts 2010; Rumbold 2006; Spinnato 2007; Villar 2009). For the other nine trials, there was insufficient information to confidently assess the risk of other sources of bias (Anthony 1996; Beazley 2005; Huria 2010; Mahdy 2004; Nasrolahi 2006; Rivas 2000; Sawhney 2000; Shahraki 2006; Xu 2010). For further details see the Characteristics of included studies tables.

Effects of interventions

See: **Summary of findings for the main comparison** Any vitamin E supplementation versus placebo, no placebo or other supplements

Twenty-one trials involving 22,129 women were identified and of these, 17 trials involving 21,856 women reported data available for analysis. Of the 17 trials included in the analyses, all supplemented women with vitamin E in combination with other supplements (vitamins or other agents).

Vitamin E in combination with other supplements compared with placebo or no control

Primary outcomes

No clear difference was found between women supplemented with vitamin E in combination with other supplements compared with

placebo for the risk of stillbirth (risk ratio (RR) 1.17, 95% confidence intervals (CI) 0.88 to 1.56, nine trials, 19,023 participants, Analysis 1.1), neonatal death (RR 0.81, 95% CI 0.58 to 1.13, nine trials, 18,617 participants, Analysis 1.2), infant death (RR 3.02, 95% CI 0.12 to 74.12, one trial, 2694 participants, Analysis 1.4) or infant hyperbilirubinaemia (RR 0.78, 95% CI 0.59 to 1.04, one trial, 725 participants, Analysis 1.7), using fixed-effect models. Substantial heterogeneity was detected for perinatal death (I^2 = 43%). When using a random-effects model, there was no clear difference in the risk of perinatal death between treatment groups (average RR 1.09, 95% CI 0.77 to 1.54, six trials, 16,923 participants, Analysis 1.3). No trials reported the outcomes haemolytic anaemia, reticulocytosis or maternal or infant haemoglobin con-

centrations.
Substantial heterogeneity was identified for the outcomes preterm birth (I^2 = 52%) and clinical pre-eclampsia (I^2 = 48%). When using a random-effects model, no clear difference was found between women supplemented with vitamin E in combination with other supplements compared with placebo or no control for the risk of preterm birth (average RR 0.98, 95% CI 0.88 to 1.09, 11 trials, 20,565 participants, Analysis 1.9) or clinical pre-eclampsia (average RR 0.91, 95% CI 0.79 to 1.06, 14 trials, 20,878 participants, Analysis 1.10). The funnel plot of preterm birth did not show any publication bias, however, the plot for clinical pre-eclampsia was visually asymmetric (Figure 3, Figure 4, respectively).

Figure 3.   Funnel plot of comparison: 1 Any vitamin E supplementation, outcome: 1.9 Preterm birth (less than 37 weeks' gestation).
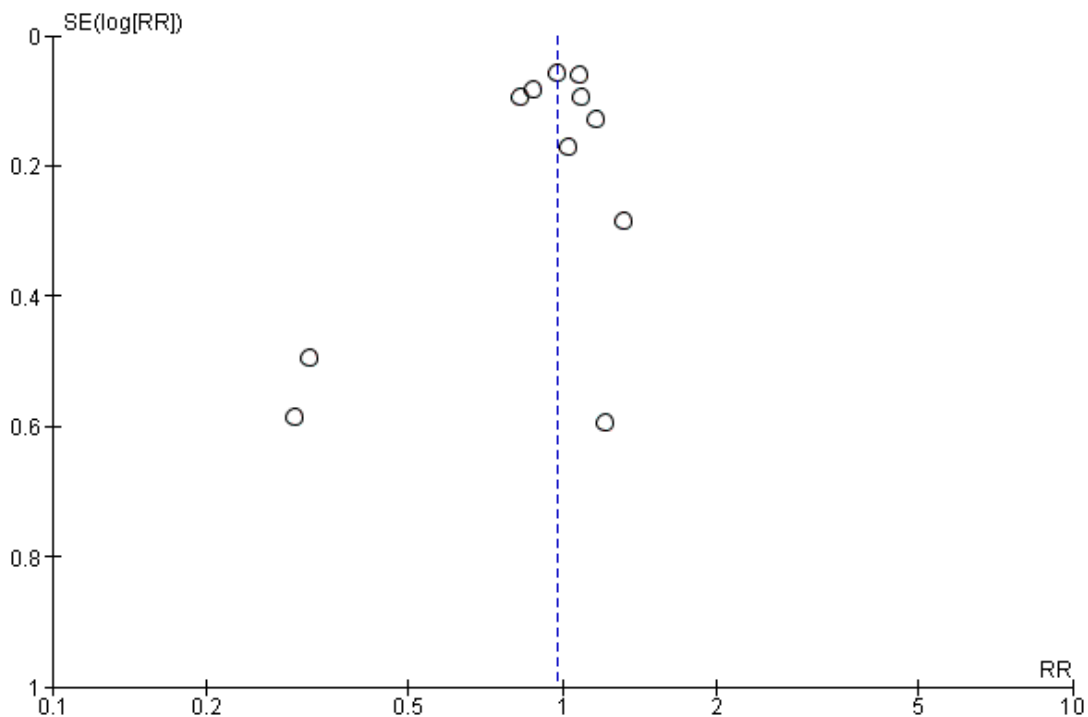
Figure 4. Funnel plot of comparison: 1 Any vitamin E supplementation, outcome: 1.10 Clinical pre-eclampsia (random-effects model).
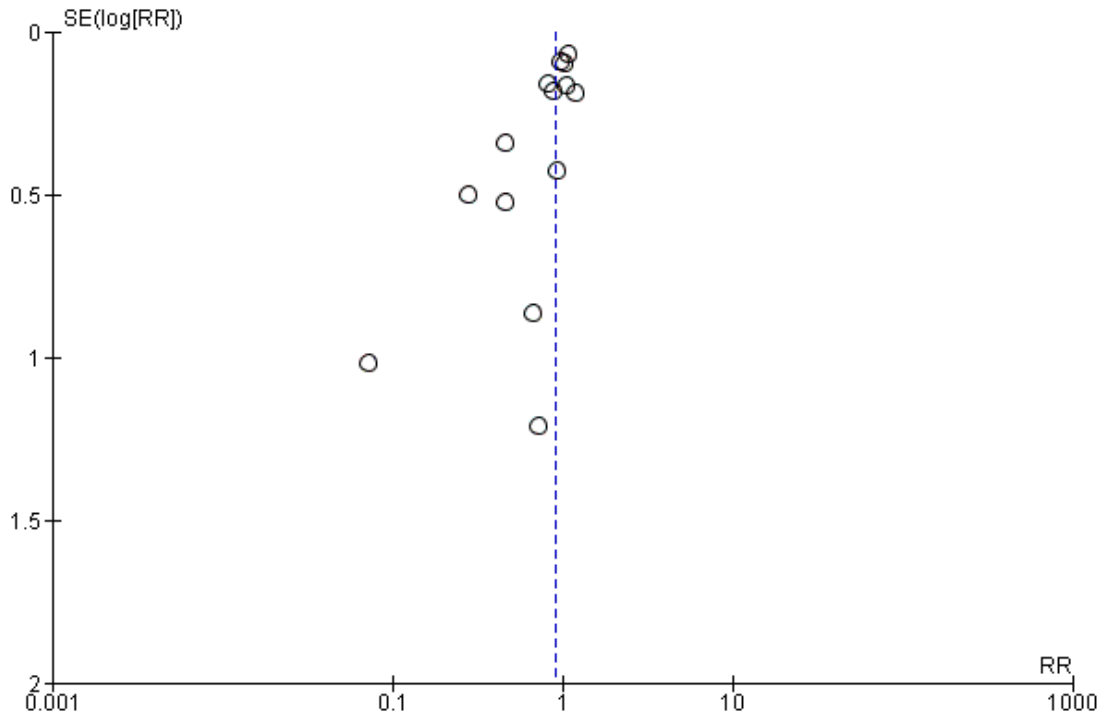
No clear difference was found for the risk of intrauterine growth restriction (RR 0.98, 95% CI 0.91 to 1.06, 11 trials, 20,202 participants, Analysis 1.11) between women supplemented with vitamin E in combination with other supplements compared with placebo or no control. Substantial heterogeneity was detected for birthweight (I^2 = 68%). When using a random-effects model, there was no clear difference between women supplemented with vitamin E in combination with other supplements compared with placebo or no control for birthweight (mean difference (MD) 22.17, 95% CI -23.01 to 67.36, 10 trials, 16,888 participants, Analysis 1.12). The funnel plots for intrauterine growth restriction did not show any publication bias (Figure 5).

Figure 5. Funnel plot of comparison: 1 Any vitamin E supplementation, outcome: 1.11 Intrauterine growth restriction (various definitions).
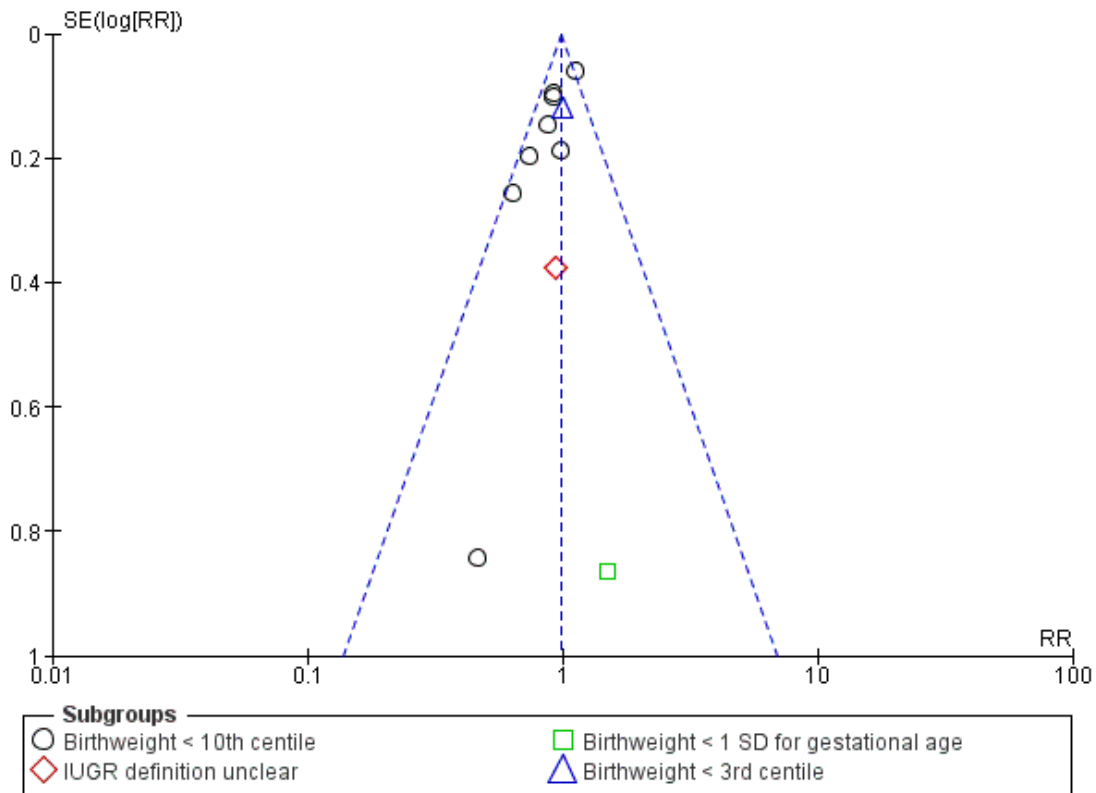
Secondary outcomes

Women supplemented with vitamin E in combination with other supplements compared with placebo had a reduced risk of placental abruption (RR 0.64, 95% CI 0.44 to 0.93, seven trials, 14,922 participants, Analysis 1.16), however there was no difference in the risk of antepartum hemorrhage (RR 1.25, 95% CI 0.85 to 1.82, two trials, 12,256 participants, Analysis 1.16).

Substantial heterogeneity was detected for preterm PROM (I² = 66%). When using a random-effects model, there was no clear difference between women supplemented with vitamin E in combination with other supplements compared with placebo for preterm PROM (average RR 1.27, 95% CI 0.93 to 1.75, five trials, 1999 participants). Conversely, women supplemented with vitamin E alone or in combination with other supplements had an increased risk of term PROM when compared with women given a placebo control (average RR 1.77, 95% CI 1.37 to 2.28, two trials, 2504 participants, Analysis 1.13).

There were no other differences in any maternal secondary out-comes between women supplemented with vitamin E in combination with other supplements compared with placebo or no control including maternal death (RR 0.60, 95% CI 0.14 to 2.51, seven trials, 17,120 participants, Analysis 1.14), any caesarean section (RR 1.02, 95% CI 0.97 to 1.07, six trials, 15,297 participants, Analysis 1.15), prelabour caesarean section (RR 1.15, 95% CI 0.85 to 1.56, two trials, 1932 participants, Analysis 1.15), induction of labour (RR 1.11, 95% CI 0.97 to 1.26, one trial, 1877 participants, Analysis 1.15), eclampsia (RR 1.67, 95% CI 0.82 to 3.41, eight trials, 19,471 participants, Analysis 1.17), renal failure or renal insufficiency (RR 1.49, 95% CI 0.55 to 4.02, two trials, 1933 participants, Analysis 1.17), disseminated intravascular co-agulation (RR 0.36, 95% CI 0.02 to 8.41, one trial, 56 participants, Analysis 1.17), or pulmonary oedema (RR 0.40, 95% CI 0.16 to 1.03. four trials, 12,569 participants, Analysis 1.17).

For the infant, substantial heterogeneity was detected for gestational age at birth, bacterial sepsis, necrotising enterocolitis and chronic lung disease or bronchopulmonary dysplasia. When using a random-effects models, there were no clear differences between

treatment groups in gestational age at birth (MD 0.15, 95% CI -0.12 to 0.43, seven trials, 13,783 participants, I² = 81%; Analysis 1.20), or the risk of bacterial sepsis (average RR 1.10, 95% CI 0.73 to 1.67, five trials, 13,324 participants; I² = 40%), necrotising enterocolitis (average RR 0.74, 95% CI 0.36 to 1.55, seven trials, 18,514 participants; I² = 45%, Analysis 1.28), or chronic lung disease/bronchopulmonary dysplasia (average RR 0.69, 95% CI 0.10 to 4.69, three trials, 3262 participants; I² = 57%, Analysis 1.25). There were no clear differences between treatment groups for any other infant outcomes including: congenital malformations (RR 1.16, 95% CI 0.83 to 1.63, four trials, 5511 participants, Analysis 1.21), or Apgar score less than seven at five minutes (RR 0.73, 95% CI 0.42 to 1.27, three trials, 3531 participants, Analysis 1.22), respiratory distress syndrome (RR 0.98, 95% CI 0.89 to 1.08, eight trials, 18,574 participants, Analysis 1.24), periventricular hemorrhage and periventricular leukomalacia (RR 0.91, 95% CI 0.58 to 1.42, six trials, 17,787 participants, Analysis 1.26) or retinopathy of prematurity (RR 1.18, 95% CI 0.72 to 1.93, six trials, 18,270 participants, Analysis 1.29).

No trials reported maternal or infant peripheral neuropathy, maternal satisfaction with care, vitamin K deficiency bleeding or haemorrhagic disease of the newborn, disability at childhood follow-up, poor childhood growth or any adverse events related to vitamin E supplementation.

None of the studies reported on adverse events that were sufficient to stop supplementation. Possible side effects of supplementation were poorly reported (Analysis 1.33). Three trials (Roberts 2010; Rumbold 2006; Xu 2010) reported on the presence of elevated liver enzymes, and there was overall no clear difference in the risk of this outcome between treatment groups (RR 1.00, 95% CI 0.71 to 1.41, three studies, 14,209 participants). An additional study (Poston 2006), reported that there was no clear difference in liver enzymes between treatment groups, however the data could not be included in the meta-analysis. One trial reported an increased risk of abdominal pain in women supplemented with vitamin E in combination with other supplements (RR 1.66, 95% CI 1.16 to 2.37, 1877 participants). However, there were no clear differences in the risk of developing other side effects including acne (RR 3.21, 95% CI 0.14 to 75.68, one trial, 56 participants), transient weakness (RR 5.36, 95% CI 0.27 to 106.78, one trial, 56 participants), or skin rash (RR 3.21, 95% CI 0.14 to 75.68, one trial, 56 participants), or any side effect (symptoms combined) (RR 1.16, 95% CI 0.39 to 3.41, one trial, 707 participants) between treatment groups.

Furthemore, one study (McCance 2010), stated in the text that there were "no adverse events or side effects attributable to supplementation."

Substantial heterogeneity for found for outcomes related to use of health service resources for the mother (Analysis 1.34). There was no clear difference between women supplemented with vitamin E in combination with other supplements compared with placebo in the risk of admission to the adult intensive care unit (average

RR 0.60, 95% CI 0.16 to 2.30; two trials, 3718, participants; I² = 45%), or hospitalisations in pregnancy (average RR 0.74, 95% CI 0.30 to 1.80, two trials, 2407 participants; I² = 61%), when using a random-effects model. There were no clear differences between treatment groups for any of the outcomes related to use of health service resources for the infant (Analysis 1.35), including: admission to the intensive care unit (RR 1.01, 95% CI 0.95 to 1.08, eight trials, 17,594 participants) and use of mechanical ventilation (RR 1.02, 95% CI 0.84 to 1.25, six trials, 8531 participants).

Sensitivity analyses by trial quality

Assessments of the treatment effects were made for the primary outcomes based on trial quality. Ten trials were judged to have a low overall risk of bias (Chappell 1999; Gulmezoglu 1997; McCance 2010; Poston 2006; Pressman 2003; Roberts 2010; Rumbold 2006; Spinnato 2007; Villar 2009; Xu 2010), for six trials the overall risk was unclear (Anthony 1996; Beazley 2005; Borna 2005; Mahdy 2004; Rivas 2000; Sawhney 2000), and five trials had a high overall risk of bias (Gungorduk 2014; Huria 2010; Kalpdev 2011; Nasrolahi 2006; Shahraki 2006). When the analyses were restricted to studies at low overall risk of bias, the risks of stillbirth, neonatal death, perinatal death, preterm birth, pre-eclampsia and intrauterine growth restriction did not change substantively to the analyses which included all trials (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6). However, for the outcomes preterm birth and clinical pre-eclampsia (Analysis 2.4; Analysis 2.5), restricting the analyses to studies at low risk of bias reduced the heterogeneity, from 52% to 32% and 48% to 25%, respectively, and there was a small reduction in the effect sizes (although both remained not statistically significant), suggesting that variation in trial quality explains some of the heterogeneity detected for these outcomes.

Subgroup analyses

Dosage of the vitamin E supplement (above or equal to/below the recommended dietary intake of 7 mg alpha-TE)

All of the included studies supplemented women with vitamin E in a dosage above the recommended dietary intake (RDI). Therefore, subgroup analyses based on dosage were not performed. Furthermore, there was limited variation in the dosages used above the RDI. For example, 15 trials used the same dose of daily 400 international units (IU) vitamin E, a further three trials gave women either daily 100 mg, 200 IU or 800 IU vitamin E, and the dose was unknown for a further three trials.

Gestation at trial entry (less than 20 weeks or greater than or equal to 20 weeks)

Five trials (Huria 2010; Kalpdev 2011; Roberts 2010; Spinnato 2007; Xu 2010) enrolled women from less than 20 weeks' gestation; five trials (Borna 2005; Gulmezoglu 1997; Gungorduk 2014; Pressman 2003; Shahraki 2006) enrolled women after 20 weeks' gestation; and the other seven trials (Beazley 2005:Chappell 1999; McCance 2010; Poston 2006; Rivas 2000; Rumbold 2006; Villar 2009) enrolled women both before and after 20 weeks' gestation. For a further four trials (Anthony 1996; Mahdy 2004; Nasrolahi 2006; Sawhney 2000), the gestation at trial entry was unknown. When the analyses were stratified across these groups, the test for subgroup differences was not significant for stillbirth, preterm birth, neonatal death, perinatal death, preterm birth and intrauterine growth restriction (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6), and the findings in the subgroups were not substantively different to the main analyses. Subgroup differences were apparent for the outcome pre-eclampsia (Chi² = 7.11, P = 0.03, I² = 71.9%), indeed the risk of pre-eclampsia was reduced in the two trials that reported pre-eclampsia and where gestation at trial entry was unknown (RR 0.32, 95% CI 0.13 to 0.79, two trials, 693 participants, I² = 0%). However, there was no significant difference in risk of pre-eclampsia in the trials that enrolled women prior to 20 weeks' (RR 1.03, 95% CI 0.91 to 1.16,five trials, 13,299 participants; I² = 0%), or those that enrolled both women before and after 20 weeks' (RR 0.90, 95% CI 0.73 to 1.12, seven trials, 6886 participants; I² = 57%). As the only significant difference was detected in trials with an unknown gestation at trial entry, the subgroup findings for pre-eclampsia are likely to reflect characteristics related to the quality of the trial, not the timing of commencement of supplementation. Collectively, these findings suggest that the treatment effect does not vary substantively by the gestation at trial entry and that differences in this characteristic do not contribute significantly to the observed heterogeneity.

Low or adequate dietary vitamin E intake prior to trial entry (low intake defined as intake less than the recommended dietary intake in that setting as measured by dietary questionnaire)

Two trials (Roberts 2010; Rumbold 2006) reported on dietary vitamin E intake of participants at trial entry. One study (Roberts 2010), was classified as including participants with "adequate intake", as the median intake in the treatment and control groups was above the RDI. The other study (Rumbold 2006), was classified as including women with "low intake" as less than half of all participants met the RDI at trial entry (43% and 42% in the treatment and control groups, respectively). One trial (Villar 2009), was designed specifically to assess the effect of vitamin E in combination with vitamin C in populations with poor nutrition, however the dietary intake of vitamin E and other micronutrients of participants was not assessed. This trial was classified as including participants with "low nutritional status", the remaining 18 trials were classified as "dietary intake unclear". Three studies (Chappell 1999; McCance 2010; Poston 2006), assessed plasma concentrations of vitamin E at baseline, and one of these trials (McCance 2010), reported information about pre-eclampsia according to baseline vitamin E status.

There were no clear differences in the risks of stillbirth, neonatal death, perinatal death, preterm birth or intrauterine growth restriction between women supplemented with vitamin E in combination with other supplements compared with placebo or no control, in any of the subgroups based on dietary intake of vitamin E (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.6).) F Furthermore, the test for subgroup differences were not significant for any of these outcomes, suggesting that the treatment effects due not differ substantively between trials in these subgroups.

For the outcome pre-eclampsia (Analysis 4.5), in a subgroup group of women with low baseline vitamin E status, the risk was reduced in women supplemented with vitamin E in combination with other supplements compared with placebo, although the result did not reach statistical significance (average RR 0.35, 95% CI 0.12 to 1.02; one trial, 95 participants). A reduced risk of pre-eclampsia was also observed among women supplemented with vitamin E in the trials where the baseline dietary intake was unclear (average RR 0.74, 95% CI 0.56 to 0.98, 10 trials, 6928 participants; I² = 52%). However, there was no observed reduction in the risk of pre-eclampsia in vitamin E supplemented women with low intake (average RR 1.20, 95% CI 0.82 to 1.75, one trial, 1877 participants), or from populations with low nutritional status (average RR 1.03, 95% CI 0.85 to 1.25, one trial, 1355 participants). There was no clear difference in the risk of pre-eclampsia between treatment groups in women with adequate intake (RR 1.07, 95% CI 0.93 to 1.24, one trial, 9969 participants), or moderate/high baseline vitamin E status (average RR 0.77, 95% CI 0.53 to 1.12, one trial, 572 participants). The test of subgroup differences was significant for this outcome (Chi² = 11.63, P = 0.02, I² = 65.6%).

The use of vitamin E in combination with other dietary supplements

Three trials supplemented women with vitamin E alone (Anthony 1996; Sawhney 2000; Shahraki 2006), however none of these trials reported any clinically meaningful information. Seventeen trials gave women vitamin E in combination with vitamin C, and two of these trials also supplemented women additionally with either allopurinol (Gulmezoglu 1997), or aspirin and fish oil (Rivas 2000). The remaining trial supplemented women with a vitamin E rich fraction of palm oil, which is likely to have contained other nutritional agents, however, no further information was provided about the content of the supplement. Therefore, as there were no trials available to assess the effect of vitamin E supplementation alone, subgroup analyses were not performed.

Women's risk status for adverse pregnancy outcomes (as defined by the authors)

Nine trials supplemented women who were at increased risk or high risk of pre-eclampsia (Beazley 2005; Chappell 1999; Kalpdev 2011; McCance 2010; Poston 2006; Rivas 2000; Spinnato 2007; Villar 2009; Xu 2010), three trials supplemented women with established pre-eclampsia (Anthony 1996; Gulmezoglu 1997; Sawhney 2000), and two trials supplemented women with established preterm PROM (Borna 2005; Gungorduk 2014). For this subgroup analysis, all 14 of these studies were classified as including women at 'high/increased risk' of adverse pregnancy outcomes. Five trials supplemented nulliparous or primiparous women (Huria 2010; Mahdy 2004; Nasrolahi 2006; Roberts 2010; Rumbold 2006), one trial supplemented pregnant women with leg cramps (Shahraki 2006), and a further trial supplemented with planned caesarean section (Pressman 2003). These remaining seven trials were classified as including women at 'low/moderate risk' of adverse pregnancy outcomes.

For the outcomes stillbirth, neonatal death, perinatal death, preterm birth, clinical pre-eclampsia and intrauterine growth restriction, there were no clear differences in the effects of vitamin E supplementation in combination with other supplements versus placebo or no control for women classified as 'high/increased risk' and for those classified as 'low/moderate' risk (Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 5.5; Analysis 5.6). Furthermore, the tests for subgroup differences were not significant for any of these outcomes. For the outcomes pre-eclampsia and preterm birth, substantial heterogeneity was present in the analyses of both of these subgroups, suggesting that heterogeneity between included studies may be due to other factors rather than just differences in baseline risk of adverse pregnancy outcomes.

DISCUSSION

Summary of main results

The results of this review, which included 21 trials involving over 21,000 women and their babies, do not support routine vitamin E supplementation in combination with other supplements in pregnancy. We found no clear differences between women supplemented with vitamin E compared with placebo or control for the risk of any primary maternal or infant outcomes including fetal, perinatal or neonatal death, preterm birth, pre-eclampsia or intrauterine growth restriction. Supplementation was associated with a reduced risk of placental abruption, which warrants further investigation. However, there was also some evidence of harm, as supplementation appeared to increase the risk of term prelabour rupture of membranes (PROM) as well as self-reported abdominal pain. There was no convincing evidence that vitamin E supplementation in combination with other supplements results in any other important benefits or harms.

Overall completeness and applicability of evidence

In this review, three trials assessed vitamin E supplementation alone in pregnancy; however, the data from these trials could not be used in the meta-analysis. Seventeen trials assessed vitamin E in conjunction with vitamin C, and one further trial gave with a vitamin E rich fraction of palm oil. Therefore, there was no information available to assess whether vitamin E supplementation alone may be beneficial or harmful for women, hence any treatment effects seen here may not be directly attributable to vitamin E.

This review provides reliable information about the impact of vitamin E supplementation in combination with other supplements on a range of maternal, perinatal and infant health outcomes. Pre-eclampsia was the most commonly reported outcome among included studies (14 trials, 20,878 participants). This is not surprising as 14 trials assessed vitamin E supplementation in combination with other supplements for the prevention of pre-eclampsia. Other commonly reported outcomes were preterm birth (11 trials, 20,565 participants), intrauterine growth restriction (11 trials, 20,202 participants), birthweight (10 trials, 16,888 participants), fetal and neonatal death (nine trials, 19,023 participants), eclampsia (eight trials, 19,471 participants), neonatal respiratory distress syndrome (eight trials, 18,574 women) and admission to the neonatal intensive care unit (eight trials, 17,782 participants). However, no trials reported any maternal and infant haematological measures (except hyperbilirubinaemia reported by one trial), vitamin K deficiency bleeding, peripheral neuropathy, maternal satisfaction with care or any possible long-term benefits or harms of supplementation for the mother. One trial (Poston 2006) reported on various measures of respiratory function (wheezing, asthma) in children aged up to two years, however, whether antenatal supplementation influences the health of children beyond two years of age is unknown .There were also scarce available data on side effects of vitamin E supplementation. One trial reported an increased risk of low abdominal pain in the vitamin supplemented group compared with a placebo control. There were no other clear differences between women supplemented with vitamin E compared with placebo or no control for any other potential side effects assessed, including elevated liver enzymes, acne, transient weakness and skin rash.

We detected substantial heterogeneity for the outcomes perinatal death, preterm birth, pre-eclampsia, birthweight, and preterm PROM. For perinatal death, excluding the trial by Villar 2009 reduced the heterogeneity to zero. Therefore, the observed heterogeneity may reflect different characteristics of participating women or differential access to maternity care, as the Villar 2009 trial involved women of low income in developing countries at risk of poor nutritional status, who may have a generally higher risk of perinatal mortality than women in the other trials who were predominantly from Western, developed, countries.

For preterm birth and pre-eclampsia, the identified heterogeneity

appears to be explained in part by variation in the quality of included studies. For example, in the sensitivity analyses, when studies at high or unclear risk of bias were excluded the magnitude of the heterogeneity was reduced markedly. Furthermore, for preterm birth, removing the trial by McCance 2010 further reduced the heterogeneity (down to I^2 = 5%). The heterogeneity that appears to be associated with McCance 2010 may reflect a higher baseline risk of preterm birth among participants in this trial compared with other trials, as McCance 2010 included women with type 1 diabetes, a known risk factor for preterm birth (Hanson 1993). Indeed the rate of preterm birth in the control group of this trial was 41%, the rate in the control group of other included studies ranged from 4% to 45% (median 23%).

In the sensitivity analyses for pre-eclampsia, removing the trial by Chappell 1999 reduced the heterogeneity to zero. It is possible that heterogeneity associated with Chappell 1999 may reflect differences in underlying risk, however the rate of pre-eclampsia in the control group (17%) was similar to that observed in other included trials (range 3% to 25%, median 15%). As Chappell 1999 was a small, positive trial, we explored the possibility of reporting bias for this outcome using a funnel plot (see Figure 4). The distribution of the results in Figure 4 are skewed, indicating that small studies reporting negative findings may be missing which could indicate reporting bias.

For preterm PROM, removing the trials by Spinnato 2007 and Xu 2010 reduced the heterogeneity to zero and the point estimate changed from RR = 1.27 to 1.02. The cause of the heterogeneity associated with these two studies is unclear. Both were judged to be at low overall risk of bias, and participants did not appear to be at high risk of preterm PROM, as the rate in the control group of both trials was lower than the rate observed in other included trials (7% to 18% versus 20% to 37%). One possibility is that there was a greater proportion of women with a history of PROM (either preterm or term) in the vitamin E group; however, this cannot be examined as information about the history of PROM among multiparous participants is not available. As these two trials are the only studies that contribute data for the outcome term PROM, the finding of an increased risk of term PROM among vitamin E supplemented women should be interpreted with caution. It should be noted that another included trial (Poston 2006), reported that there was no difference in the risk of either preterm or term PROM between treatment groups, however, individual data were not reported so this trial did not contribute to the meta-analysis for those outcomes. Further observational research investigating the role of vitamin E in the development of preterm and term PROM is warranted.

We also undertook pre-specified subgroup analyses exploring the effect of variation in baseline risk of adverse pregnancy outcomes. Approximately two-thirds of all trials included women considered to be at high or increased risk of adverse outcomes (mostly pre-eclampsia). For all of the primary outcomes, the effect sizes did not vary substantially between women at high/increased risk and women at low/moderate risk, suggesting that there are no benefits of supplementation in particular subgroups based on underlying risk.

We also undertook other subgroup analyses to explore the impact of variation in timing of commencement of supplementation (i.e. gestation at trial entry) and adequacy of dietary intake of vitamin E prior to trial entry. While there was substantial variation in the gestation at trial entry across all of the included studies, the subgroup analyses did not reveal any substantial differences in the effect size between trials enrolling women prior to 20 weeks', after 20 weeks' or that included women both prior to and after 20 weeks' gestation. This suggests that there is no benefit of commencing supplementation either earlier or later in pregnancy.

Whether vitamin E supplementation is beneficial for women with low or inadequate vitamin E intake is unclear. Only two studies reported information specifically about women's dietary intake of vitamin E at trial entry, and in the subgroup analyses including these trials, there were no apparent benefits of vitamin E supplementation either in women with low or adequate intake. One study (Villar 2009) was undertaken in women from populations with a presumed low dietary intake of vitamin E, based on dietary information collected in previous studies of clinic attendees. There was no clear difference in the pattern of risks of adverse outcomes in these women either. One trial (McCance 2010), reported information about pre-eclampsia according to baseline plasma vitamin E status. In this trial, there appeared to be a reduced risk of pre-eclampsia in women with a low baseline vitamin E intake, although the result was of borderline statistical significance and should be interpreted with caution due to the small number of women in this subgroup (n = 95).

Subgroup analyses exploring the impact of vitamin E dosage and use of vitamin E combined with other supplements were planned but could not be undertaken due to insufficient data in each subgroup.

Quality of the evidence

The overall risk of bias is low to unclear for most of the studies, however, there were some high quality, large trials that were heavily weighted in the analysis. Five trials were judged to be at high risk of bias.

The quality of the evidence using GRADE was high for preterm birth, intrauterine growth restriction and placental abruption, moderate for stillbirth and clinical pre-eclampsia, and low for preterm PROM (Summary of findings for the main comparison). The outcomes were downgraded due to wide confidence interval crossing the line of no effect, statistical heterogeneity, and publication bias.

Potential biases in the review process

We followed the Cochrane Pregnancy and Childbirth Group search strategies, which includes a search of the Trials Register that is updated weekly to monthly from a range of databases as well as handsearches from selected journals and proceedings of major conferences. Therefore, it is unlikely that studies that have been missed, although it is possible that studies that have not been published could be missing. Should any further studies be identified, we will include them in future updates of the review. We also followed the Cochrane Pregnancy and Childbirth Group recommended review process to reduce potential biases, which included having at least two review authors independently assessing identified studies, extracting data and evaluating risk of bias.

Agreements and disagreements with other studies or reviews

The findings of this review are in agreement with several meta-analyses examining the effects of vitamin C and E supplementation for the prevention of pre-eclampsia and other maternal and perinatal complications (Basaran 2010; Conde-Agudelo 2011). The finding of a 36% reduction in the relative risk of placental abruption among vitamin E supplemented women compared with placebo or no control warrants further investigation. There is some limited evidence of serum markers of oxidative stress as well as low serum levels of vitamin E in women with placental abruption (Incebiyik 2015; Sharma 1986), suggesting a biologically plausible role for vitamin E supplementation. However, lower serum levels of other antioxidants including vitamin C have also been demonstrated (Sharma 1985), therefore, it is unclear whether the result observed in this review is due to vitamin E or C or the combination of both agents. Further observational research examining the underlying pathways to placental abruption is required, before any firm conclusions can be drawn about this finding.

AUTHORS' CONCLUSIONS

Implications for practice

There is now a large body of evidence from randomised trials involving over 21,000 women assessing the effects of vitamin E supplementation in combination with other supplements including vitamin C in pregnancy. The available data do not support routine vitamin E supplementation in combination with other supplements for the prevention of fetal or neonatal death, preterm birth, pre-eclampsia, or intrauterine growth restriction for all women or for women at high risk of adverse pregnancy outcomes. Supplementation was associated with a reduced risk of placental abruption, this should be explored in further research examining the specific role of vitamin E in the etiology of placental abruption. There was some evidence of harm, as vitamin E supplementation appeared to increase the risk of term PROM and self-reported abdominal pain.

Implications for research

The reduction in placental abruption requires further assessment. Future research should be conducted to examine whether the observed effects for placental abruption are due to vitamin E or the influence of other agents including vitamin C. Long-term follow-up studies of women and children enrolled in the current trials are required to determine whether there are any longer term benefits or harms of vitamin E supplementation. Further research is also required to examine the effect of supplementation in women with a low or inadequate intake of vitamin E prior to and in early pregnancy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Anthony 1996

Methods	A double-blind, placebo-controlled trial of vitamin E supplementation was conducted. All patients were managed in the same unit by the same team using standardised protocols over the last 3 years
Participants	First recruited 73 women undergoing conservative antenatal management of pre-eclampsia
Interventions	Vitamin E supplementation versus placebo.
Outcomes	1. Duration of conservative management 2. Indications for delivery 3. Renal function, protein excretion and platelet levels
Notes	Recruitment was still open at the time of publishing the abstract, and final analysis was presented on the day of poster session. No data incorporated in the analysis of this review Setting: South Africa.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" stated in abstract, no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statistically significant differences between the groups but did not identify any details and the number of patients in each comparison groups
Selective reporting (reporting bias)	Unclear risk	Protocol was used but no data given in this abstract.
Other bias	Unclear risk	Only abstract available.

Beazley 2005

Methods	Treatment allocation: unclear, women were "randomised".
	Blinding of outcome assessment: "double blind" stated.
	Documentation of exclusion: 9 (8%) women were lost to follow-up
	Use of placebo control: placebo control.
Participants	109 women were recruited into the study. Inclusion criteria: women at "high risk of pre-eclampsia" including those with previous pre-eclampsia, chronic hypertension, pregestational diabetes and multiple pregnancy. Nil exclusion criteria stated. Women were randomised at 14-20 weeks' gestation to receive either daily vitamin E and C (n = 54) or placebo (n = 55)
Interventions	Women randomised to the treatment group received daily 400 IU vitamin E in addition to 1000 mg vitamin C. No details on the content of the placebo were given
Outcomes	1. Pre-eclampsia (not defined)
	2. GA at delivery (weeks)
	3. Preterm birth (< 37 weeks' gestation)
	4. Birthweight
	5. Birthweight < 10 centile
	6. Total antioxidant status and 8-isoprostane
Notes	Dosage: daily 400 IU vitamin E, above RDI.
	GA at trial entry: <= 20 weeks' gestation.
	Dietary vitamin E intake before trial entry: unclear, no dietary information reported
	Type of supplement: vitamin E given in addition to vitamin C
	Women's risk status: women were at high risk of pre-eclampsia
	Intention-to-treat analyses: stated that analyses were intention-to-treat, however losses to follow-up were not included in the totals. Available case analysis
	Sample size calculation: none reported.
	Compliance: unclear, no details given.
	Location: United States of America.
	Timeframe: unclear.
	The trial was stopped early after cessation of funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "double-blind, randomized clinical trial" stated, but no details about sequence generation provided
Allocation concealment (selection bias)	Unclear risk	As above, no details provided about method of allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind" and "placebo" stated but no further details provided

Beazley 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided about blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 (8%) women were lost to follow-up or withdrew, 6 (11%) in control group, and 3 (5%) in the vitamin group
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	Unclear risk	No details provided about the baseline characteristics of each group

Borna 2005

Methods	A randomised controlled trial conducted from September 2002 to September 2003 at a teaching hospital in Tehran, Iran Block randomisation method was used for allocation of participants
Participants	60 women with singleton pregnancy who had preterm premature rupture of membrane at 26 to 34 weeks' gestation were enrolled to the study Exclusion criteria included chorioamnionitis, non-reassuring fetal status on admission, obstetric indication for immediate delivery, delivery within 24 hour of admission, major congenital anomalies, and fetal growth restriction
Interventions	Intervention group (n = 30) received tablets containing 500 mg of vitamin C and 400 IU of vitamin E daily Control group (n = 30) received placebo tablets similar to the intervention group All women received prophylactic antibiotics (ampicillin 2 g and erythromycin 250 mg div q6h for first 48 hours, followed by amoxicillin 250 mg and erythromycin base 333 mg po tid for 5 days). All women received 2 injections of 12 mg betamethasone during first 24 hours of admission
Outcomes	Study protocol was not available and following outcomes were reported: 1. Latency (mean, SD) 2. Birthweight (mean, SD) 3. GA at delivery (mean, SD) 4. Amniotic fluid index <= 5 cm at admission (number, percentage) 5. Amniotic fluid index <= 5 cm after the beginning of labour (number, percentage) 6. Caesarean section due to fetal distress (number, percentage) 7. Chorioamnionitis (number, percentage) 8. Postpartum endometritis (number, percentage) 9. RDS (number, percentage) 10. NICU admission (number, percentage) 11. Neonatal sepsis (number, percentage) 12. Neonatal mortality (number, percentage)
Notes	

Borna 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Block randomisation methods used, but no details of sequence generation
Allocation concealment (selection bias)	Unclear risk	No details provided about any method of concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Randomization was blinded to both patients and caregivers" Quote: "The control group received placebo tablets similar to those of vitamins C and E at the same frequency"; therefore, the review authors believe blinding of patients and caregivers was probably maintained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No specific information provided about blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided about attrition.
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available.
Other bias	Low risk	Baseline characteristics were similar between groups.

Chappell 1999

Methods	Treatment allocation: a computer-generated randomisation list using blocks of 10 was given to the hospital pharmacy departments. Researchers allocated the next available number to participants and women collected the trial tablets from the pharmacy department Blinding of outcome assessment: women, caregivers and researchers were blinded to the treatment allocation until recruitment, data collection and laboratory analyses were complete Documentation of exclusion: pregnancy outcome data were reported according to treatment allocation for all women randomised Use of placebo control: placebo control.
Participants	283 women were recruited into the study. Inclusion criteria: abnormal Doppler waveform in either uterine artery at 18-22 weeks' gestation or a history in the preceding pregnancy of pre-eclampsia necessitating delivery before 37 weeks' gestation, eclampsia or the syndrome of HELLP.

	Exclusion criteria: heparin or warfarin treatment, abnormal fetal-anomaly scan or multiple pregnancy. Women were randomised at 18-22 weeks' gestation; however, women with a previous history who were identified at an earlier stage were randomised at 16 weeks' gestation. Women with abnormal Doppler waveform analysis returned for a second scan at 24 weeks' gestation, those with a normal waveform at this time stopped treatment and were withdrawn from the study. The remaining women who had persistently abnormal waveforms and those with a previous history or pre-eclampsia remained in the study and were seen every 4 weeks through the rest of pregnancy. 1512 women underwent Doppler screening, 273 women had abnormal waveforms and, of these, 242 women consented to the study. An additional 41 women who had a history of pre-eclampsia consented. 283 women were randomised to either the vitamin C and E group (n = 141) or the placebo group (n = 142), 72 women had normal Doppler scans at 24 weeks' gestation and 24 women did not return for a second scan and were withdrawn. A further 27 women withdrew from the trial after 24 week's gestation for various reasons. In total, 160 women completed the trial protocol until delivery, 79 in the vitamin C and E group and 81 in the placebo group. Pregnancy outcome data were presented for all women randomised (n = 283) as well as only for those women completing the trial protocol (n = 160)
Interventions	Women randomised to the vitamin E and C group received capsules containing 400 IU natural source vitamin E daily and tablets containing 1000 mg vitamin C daily. Women randomised to the placebo group received capsules containing soya bean oil and tablets containing microcrystalline cellulose that were identical in appearance to the vitamin E capsules and vitamin C tablets. After 24 weeks' gestation women were seen every 4 weeks, and blood samples were taken at each visit
Outcomes	1. Ratio of PAI-1 to PAI-2 2. Pre-eclampsia (defined according to the International Society for the Study of Hypertension in Pregnancy guidelines) 3. Placental abruption 4. Spontaneous preterm delivery (< 37 weeks' gestation) 5. Intrauterine death 6. SGA infants (on or below the 10th centile) 7. Mean systolic and diastolic blood pressure before delivery 8. GA at delivery (median, IQR) 9. Birthweight (median, IQR) 10. Birthweight centile (median, IQR) 11. Mean plasma ascorbic acid and alpha-tocopherol concentrations during gestation 12. Biochemical indices of oxidative stress and placental function
Notes	Dosage: 400 IU natural source vitamin E daily, above RDI. GA at trial entry: between 16 to 22 weeks' gestation. Dietary vitamin E intake before trial entry: unknown, not assessed Type of supplement: vitamin E given in addition to vitamin C Women's risk status: women were at "high risk for pre-eclampsia" Intention-to-treat analyses: performed, pregnancy outcome data were available for all women randomised, and results were presented according to initial treatment allocation Sample size calculation: the study had 80% power to detect a 30% reduction in PAI-1

	Compliance: not specifically reported. "Within the treated group, plasma ascorbic acid concentration increased by 32% from baseline values and plasma alpha-tocopherol increased by 54%." Location: London, United Kingdom. Timeframe: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomisation list was drawn up by the statistician, with randomisation in blocks of ten"
Allocation concealment (selection bias)	Low risk	Researchers allocated the next available number to participants and women collected the trial tablets directly from the pharmacy department
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and researchers were blinded to the treatment allocation until recruitment, data collection and laboratory analyses were complete. Placebo control used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women, caregivers and researchers were blinded to the treatment allocation until recruitment, data collection and laboratory analyses were complete. Placebo control used
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	Low risk	Baseline characteristics were similar between groups.

Gulmezoglu 1997

Methods	Treatment allocation: "The treatment packs were randomised by computer generated random numbers in blocks of ten". Randomisation was carried out by an independent researcher who was not involved in the study, and medications were placed in consecutively numbered sealed opaque bags Blinding of outcome assessment: women, caregivers and researchers were blinded to the treatment allocation Documentation of exclusion: no exclusions documented. Use of placebo control: placebo control.
Participants	56 women were recruited into the study. Inclusion criteria: women who were admitted to the antenatal wards with a diagnosis of severe pre-eclampsia, as defined by 2+ proteinuria on urine dipstix testing (in at least 2 consecutive tests 4 to 6 hours apart) , with a blood pressure of 160/110 mmHg, or 3+ proteinuria with blood pressure >= 150/100 mmHg; between 24 and 32 weeks' gestation; with a single live fetus; with no systemic disorder (such as diabetes or systemic lupus erythematosus) and no allergy to study medications. Women were approached when they were eligible for conservative management, as defined by an absence of significant renal impairment, the HELLP syndrome or thrombocytopenia alone. Conservative management consisted of advising women to stay in hospital until delivery, with weekly betamethasone injections up to 32-34 weeks' gestation, and with frequent fetal and maternal monitoring. Exclusion criteria: none stated. 59 women were approached and counselled about the study, of which 56 women gave informed written consent, and allocated to either the vitamin group (n = 27) or placebo (n = 29)
Interventions	Women randomised to the vitamin group received twice daily 400 IU vitamin E (800 IU daily total), 500 mg vitamin C (1000 mg daily total) and 100 mg allopurinol (200 mg daily total). Women randomised to the placebo group received the same number of tablets that were identical to the vitamin C and allopurinol tablets. Vitamin C placebos were used as placebos for vitamin E because it was not possible to obtain 2 separate sets of placebos from the supplier; however, the vitamin E tablets and their placebos were slightly different. To preserve blinding all medications were placed in dark brown coloured bottles and sealed opaque paper bags
Outcomes	1. Delivery within 14 days 2. Maternal deaths 3. Serious maternal complications (pulmonary oedema, eclampsia, HELLP syndrome, DIC, renal failure) 4. Placental abruption 5. Prelabour caesarean section 6. Use of antihypertensives 7. Stillbirth 8. Apgar score < 7 at 1 minute and < 7 at 5 minutes 9. Umbilical artery pH < 7.2 10. Admission to intensive care unit 11. Mechanical ventilation 12. Neonatal death 13. Perinatal death 14. Birthweight (median, range)

	15. Lipid peroxide and vitamin E levels
	16. Haematological and renal function parameters
	17. Placental lipid peroxide and glutathione levels

Notes	Dosage: 800 IU vitamin E, above RDI.
	GA at trial entry: > 20 weeks' gestation.
	Dietary vitamin E intake before trial entry: unclear, no dietary information reported
	Type of supplement: vitamin E given in addition to vitamin C and allopurinol
	Women's risk status: women had established early onset severe pre-eclampsia
	Intention-to-treat analyses: all data were reported according to women's treatment allocation, and were available for all women for the primary outcome. There were missing data for the outcomes Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, umbilical artery pH < 7.2, and the lipid peroxide and vitamin E levels and haematological and renal function parameters
	Sample size calculation: a sample size of 54 women had 80% power to detect a halving in the number of women needing delivery within 14 days, from 80% to 40%
	Compliance: compliance in the vitamin group was estimated at 84%, 89%, 93% for the vitamin E, vitamin C and allopurinol tablets. For the placebo group compliance was 75%, 100% and 86% for the vitamin E, vitamin C and allopurinol placebo tablets
	Location: Johannesburg, South Africa.
	Timeframe: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "treatment packs were randomised by computer generated random numbers in blocks of ten"
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was done by an independent researcher who was not involved in the study" and "medications (active or placebo) were placed in consecutively numbered sealed opaque paper bags"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and researchers were blinded to the treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women, caregivers and researchers were blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data were reported according to women's treatment allocation, and were available for all women for the primary outcome. Some missing data for secondary outcomes

| Selective reporting (reporting bias) | Unclear risk | Study protocol not available. |
| Other bias | Low risk | Baseline characteristics were similar between groups. |

Gungorduk 2014

Methods	A randomised controlled trial conducted between January 2011 and November 2011 at a teaching hospital in Istanbul, Turkey Prior to the recruitment, code was generated with computer and stored in a sealed, consecutively numbered opaque envelope Stratification of randomisation by GA (24.0-25.9, 26.0-27.9, 28.0-29.9, 30.0-31.9, and 32.0-33.9 weeks) was carried out Both participants and caregivers were not blinded.
Participants	246 women with singleton pregnancy who had non-anomalous fetus and preterm premature rupture of membranes at 24 to 34 weeks' gestation were enrolled to the study All patients were admitted to the hospital. Exclusion criteria included fetus anomalies, chorioamnionitis, within 14 days of amniocentesis or cervical cerclage placement, multiple gestation, obstetric indication for immediate delivery, intrauterine fetal death at the time of presentation Patients who had active preterm labour were also excluded.
Interventions	Intervention group received 1000 mg of vitamin C (ascorbic acid) and 400 IU of vitamin E (RRR α-tocopherol acetate) Control group received placebo. Intervention was initiated within 1 hour after the diagnosis of rupture of membrane Amoxicillin 2 g/d for 7 days was administered as prophylaxis. In case of allergy to amoxicillin, erythromycin 1 g/d for 7 days was used 2 doses of 12 mg IM betamethasone injection were administered at interval of 24 hours
Outcomes	Study protocol was not available and following outcomes were reported **Primary outcome** Latency period until delivery **Secondary outcomes** 1. Birthweight 2. Mode of delivery 3. Occurrence of clinical chorioamnionitis 4. Postpartum endometritis 5. Early onset neonatal sepsis 6. Grade 3 to 4 IVH 7. Stage 2 to 3 NEC 8. Admission to the NICU 9. RDS 10. Birth within 48 hours of randomisation 11. Birth within 7 days of randomisation 12. Composite perinatal morbidity/mortality (defined as the occurrence of RDS, grade

	III or IV IVH, NEC, neonatal sepsis, or perinatal death
Notes	Sample size was calculated based on hospital experience; 6 days latency period with standard deviation of 3 days. 112 participants needed to be recruited to detect 50% increase in latency period (type I error 5% and power 80%) Intention-to-treat analysis was carried out. Figure in paper states that 229 women were randomised, however, the sum of the 2 groups analysed is 246

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated code prepared prior to recruitment"
Allocation concealment (selection bias)	Low risk	Quote: "sealed, consecutively numbered, opaque envelope" used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "identical supplements could not be used for the control and experimental groups; therefore the patients and researchers were not blinded to the conditions"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessors was not stated but is unlikely to have occurred (see above quote). The primary outcome was latency to delivery, which could be influenced by biased clinical decisions about timing of delivery based on knowledge of treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 (1%) patients were lost to follow-up, and the number (and reason) for losses to follow-up was balanced between the 2 groups
Selective reporting (reporting bias)	Low risk	Study protocol available and all outcomes reported.
Other bias	Low risk	Baseline characteristics similar between groups.

Huria 2010

Methods	A randomised controlled trial conducted during June 2006 to August 2007 at a medical college hospital in Chandigarh, India
Participants	285 women attending antenatal clinic were enrolled to the study Inclusion criteria: women who gave consent to participate in the study, primigravida, singleton pregnancy, willing to deliver at the study hospital Exclusion criteria: women with blood pressure higher than 130/85 mmHg, using antihypertensive medication, proteinuria, intention to deliver at other hospital, known complication such as diabetes and hypothyroidism, known fetal malformations, using more than 150 mg of vitamin C or more than 75 IU of vitamin E, using NSAID 145 were allocated to the intervention group and 140 to the control group
Interventions	Intervention group received 1000 mg vitamin C and 200 mg vitamin E. Control group received placebo All participants received 100 doses of iron and folic acid from 12 weeks of pregnancy
Outcomes	A study protocol was not available and following outcomes were reported: 1. Gestational hypertension or pre-eclampsia 2. IUGR 3. Preterm birth 4. Caesarean section Preterm birth defined as "birthweight less than 2.5kg" in text, but in one table is reported according to gestation at delivery
Notes	Inconsistent description of vitamin E dose; both "mg" and "IU" were used Although the report claimed that "women identified at the risk of preeclampsia" were studied, no such description could be found in the method section There are discrepancies between the reported numbers lost to follow-up and the final numbers included in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "random allocation of study subjects" stated, but no details on sequence generation provided
Allocation concealment (selection bias)	Unclear risk	No details provided about any method of concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blinding was ensured by random allocation of study subjects and coding of drugs". No further details were provided to permit an assessment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Double blinding was ensured by random allocation of study subjects and coding of drugs". No further details were

Huria 2010 (*Continued*)

		provided to permit an assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for 72 (25%) participants missing, 34 (23%) in vitamin group and 38 (27%) in control group. Of the 34 women in the vitamin group, 18 were "lost to follow up" and 16 delivered elsewhere. Of the 38 women in the control group, 16 were "lost to follow up" and 22 delivered elsewhere. The reasons for delivery elsewhere were not provided. Although the number of women lost to follow-up in each group was similar, given the magnitude of the effect size for some outcomes (e.g. preterm birth), the review authors suspect that there may be clinically relevant bias. For example, the risk of preterm birth was 14.7% in control and 4.7% in the vitamin group, which could reflect women in the vitamin group who are in preterm labour being transferred to another hospital for delivery
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available.
Other bias	Unclear risk	Information about baseline characteristics was not available

Kalpdev 2011

Methods	A randomised controlled trial conducted between June 2005 to June 2007 in Chandigarh, India Computer-generated number was used for randomisation.
Participants	50 women between 13 and 19 weeks of gestation were enrolled to the study. 25 were allocated to intervention group and 25 to control group Inclusion criteria: women with essential hypertension who booked in the Hypertensive Disorders of Pregnancy Clinic, singleton pregnancy at GA between 16 to 22 weeks, giving consent for participation Exclusion criteria: multifetal pregnancy, known fetal abnormalities, use of illicit drug or alcohol during pregnancy, intention to deliver outside of study site, renal hypertension, proteinuria, already taking vitamin C and E
Interventions	Intervention group received 500 mg vitamin C twice daily (1000 mg/day) and 400 IU natural vitamin E once daily Control group did not receive vitamins (not placebo-controlled trial) All women received iron, folic acid and calcium.

Outcomes	Study protocol was not available but following outcomes were evaluated **Primary outcome** Development of superimposed pre-eclampsia **Secondary outcomes** *Maternal* 1. Aggravation of hypertension 2. Need for admission 3. Need to increase antihypertensive drugs 4. Incidence of HELLP 5. Low platelet count 6. Liver enzyme equal or greater than 5 times in absence of obstetric cholestasis *Fetal/neonatal* 1. Incidence of growth retardation 2. Gestation at delivery 3. Birthweight 4. Stillbirth 5. Apgar score at birth
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Women were randomized using computer-generated numbers"
Allocation concealment (selection bias)	Unclear risk	No details provided about method of concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo control and no details of blinding provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of blinding provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 (12%) participants were not included in analyses, 3 in each treatment group, but no details about the reasons for missing data for these women
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available.
Other bias	Low risk	No reported differences between groups at baseline.

Mahdy 2004

Methods	A randomised placebo-controlled trial.
Participants	Interim analysis was performed on 113 primigravida women, 46 were allocated to intervention group, 67 were in control group
Interventions	Intervention group: tocotrienol-rich fraction (TRF) of palm oil Control group: placebo.
Outcomes	**Primary outcomes** 1. Pregnancy-induced hypertension 2. Pre-eclampsia
Notes	Result of interim analysis. Poster session abstract only. Setting: Malaysia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized, double blind placebo-controlled clinical trial"; no further details given (only abstract available)
Allocation concealment (selection bias)	Unclear risk	Not described in abstract.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" stated in abstract, no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind" stated in abstract, no further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to assess attrition bias.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess reporting bias.
Other bias	Unclear risk	Insufficient information to assess other bias.

McCance 2010

Methods	A randomised placebo-controlled trial conducted in 25 UK antenatal metabolic clinics Enrolment was carried out between April 2003 and June 2008. A randomisation sequence was generated by Victoria Pharmaceuticals using computer software (PRISYM ID, version 1.0009). The sequence was stratified by clinic with balanced block size of 8 Both participants and study personnel were blinded to the allocation status until the completion of the trial
Participants	Inclusion criteria: pre-existing type 1 diabetes before pregnancy, GA between 8 and 22 weeks at presentation, singleton pregnancy, age 16 years or older Exclusion criteria: those who did not give consent, already enrolled in other study, warfarin treatment, known history of drug misuse, taking vitamin supplements containing daily dose of more than 500 mg vitamin C or more than 200 IU vitamin E 1621 women were assessed for eligibility, 859 were excluded, and 762 were randomised into 2 groups; 379 in intervention group and 383 in control group. 1 participant in control group was lost to follow-up with consent withdrawal
Interventions	Intervention group received 1000 mg vitamin C and 400 IU vitamin E daily from recruitment until delivery Control group received matched placebo daily.
Outcomes	**Primary outcome** Pre-eclampsia **Secondary outcomes** 1. Placental and endothelial activation 2. Birthweight centile Postnatal follow-up - weight, length and head circumference are reported as SD scores, assessed between 6 to 12 weeks of age, however the data were not reported in a suitable format to be included in the meta-analysis Results include the following statement: "We noted no adverse events or side effects attributable to supplementation with vitamin C or E in mothers or infants."
Notes	ISRCTN27214045

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation sequence generated in advance by Victoria. Pharmaceuticals using PRISYM ID software".
Allocation concealment (selection bias)	Low risk	Quote: "randomisation sequence was stratified by centre with balanced blocks of eight patients, and was held by Victoria Pharmaceuticals. Individual sealed envelopes containing treatment allocations were given to trial pharmacists in every centre, allowing

		treatment group to be revealed in a clinical emergency"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment allocation was masked from all trial personnel and participants until trial completion", and identical looking placebo tablets were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary outcome data missing for 1 participant (placebo group) who withdrew consent. Quote: "749 women were assessed for pre-eclampsia, by original assigned group (375 vitamin, 374 placebo). There were 12 deviations from the inclusion and exclusion criteria--eight women were enrolled outside the 22-week cutoff for gestation (all were within 4 days of this threshold) and 4 patients were later reclassified as having type 2 diabetes. All 12 women were included in the analysis"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the study protocol were reported
Other bias	Low risk	Quote: "Although most maternal baseline characteristics did not differ between groups, history of pre-eclampsia, hypertension, antihypertensive treatment, and microalbuminuria were more common in the placebo group than in the vitamin group" Although these factors were not adjusted for in the analyses, the possible impact of this would be to overestimate the treatment effect, however, no differences were found between the treatment groups, therefore the risk of likely to be low

Nasrolahi 2006

Methods	Randomised controlled trial conducted from March 2003 to March 2004 in Hamadan, Iran
	Participants were divided into 2 groups based on the first day of visit to the prenatal care. Women visited on even numbered days were put into the treatment group, whereas those visited on odd days were put into the control group
Participants	580 women were enrolled, 290 in intervention group and 290 in control group
	Inclusion criteria
	Primiparous women
	Singleton pregnancy
	Exclusion criteria
	History of underlying hypertension
	Obese with BMI greater than 35
	Smoker
	Multifetal pregnancy
	Molar pregnancy
	History of previous abortion
Interventions	Intervention group received daily dose of 400 unit vitamin E and 1 g vitamin C until the end of pregnancies
	Control group received ferrous sulphate during pregnancy.
Outcomes	1. Pre-eclampsia
	2. Gestational age at birth
	3. Birthweight
Notes	Translated from Persian to English by Ross C Poletti in December 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: participants were "divided into two groups based on the first day of prenatal admission"
Allocation concealment (selection bias)	High risk	Quote: participants were "divided into two groups based on the first day of prenatal admission"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo control, and no further details of blinding, therefore, the review authors believe blinding is unlikely to have occurred
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data presented for all participants.
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	Unclear risk	Treatment groups were similar for maternal age at baseline, no other characteristics were presented

Poston 2006

Methods	A randomised controlled trial (the Vitamins in Pre-eclampsia [VIP] trial) was conduced between Aug 6, 2003, and June 27, 2005 to which we enrolled women with clinical risk factors for pre-eclampsia from 25 UK hospitals in 10 geographical areas. The last baby was delivered on Dec 3, 2005. Eligible women could be referred to trial centres from any location in the UK. 13 women were recruited in Amsterdam, Holland
Participants	2410 women in GA 14-21 weeks plus 1 or more of the following risk factors: pre-eclampsia in the pregnancy preceding the index pregnancy, requiring delivery before 37 completed weeks' gestation at increased risk of pre-eclampsia from 25 UK hospitals in 10 geographical areas Text states that 2404 women were "validly randomised".
Interventions	1 tablet and 1 capsule daily of vitamin C and vitamin E and placebo from the second trimester of pregnancy until delivery Custom Pharmaceuticals manufactured the vitamin C (1000 mg) and identical placebo tablets (microcrystalline cellulose with addition of tartaric and citric acid to provide similar acidic taste), and Banner Pharmacaps provided identical gelatin capsules containing 400 IU natural source vitamin E (RRR α tocopherol) or placebo (sunflower seed oil) . DHP Investigational Medicinal Products Clinical Trial Supplies (Crickhowell, Powys, Wales, UK) packaged the tablets and capsules sealed in blister strips each with 1 week's supply, according to the randomisation sequence provided Each pack contained a 7-month supply of trial medication. The midwives told women to take 1 tablet and 1 capsule daily, and asked participants to leave unused tablets or capsules in the blister strip. Postage prepaid envelopes were provided for return of blister strips to the research midwife at intervals of 4 weeks. If not received, the computer program generated a prompt to remind the women (by telephone) to return that month's packs. Participants were also given a postage pre-paid postcard to notify the research midwife of delivery
Outcomes	**Primary outcome** Pre-eclampsia **Secondary outcomes** Severe pre-eclampsia, gestational hypertension, severe gestational hypertension, antenatal onset of pre-eclampsia, postpartum onset of pre-eclampsia, delivery for pre-eclampsia before 37 weeks' gestation, delivery for pre-eclampsia before 34 weeks' gestation, HELLP syndrome, eclampsia, severe proteinuria (> 5 g in 24 hours), magnesium sulphate for pre-eclampsia, intravenous anti-hypertensive therapy, antenatal steroids, maternal death,

	antenatal inpatient nights (mean, SD), LBW (< 2·5 kg) and small size for GA (< 5th centile) The study also reported on preterm and term PROM (no differences observed between groups), however no raw data were provided so the study did not contribute to the meta-analysis for those outcomes The study also reported outcomes related to respiratory function in children at 2 years of age
Notes	Additional analyses were carried out that were not in the predefined analysis plan with selecting patients with similar rates of pre-eclampsia. This trial was registered an International Standard Randomised Controlled Trial, number ISRCTN 62368611 Location: UK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation sequence was blocked..by centre in groups of two to ten individuals... The trial statistician (PTS) wrote the computer program that generated the sequence and a statistician not involved with the trial ran it with a new random number sequence"
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was undertaken online and the participant allocated a locally stored pack of trial medication identified by a centre specific and participant-specific number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All women and trial staff blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All women and trial staff blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 (0.4%) participants were lost to follow-up and the proportion of missing data was similar between groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported. Study protocol was available (ISRCTN 62368611)

Other bias	Low risk	Baseline characteristics were similar between groups.

Pressman 2003

Methods	In a randomised, double-blind study conducted in 20 women scheduled to undergo planned caesarean delivery at term who met specified inclusion and exclusion criteria randomly received a daily prenatal vitamin with or without 400 IU of vitamin E and 500 mg of vitamin C, starting at 35 weeks' gestation
Participants	20 women included planned caesarean section at term (38 weeks' or later) at Strong Memorial Hospital, USA. Exclusion criteria included maternal complications requiring delivery before scheduled caesarean delivery, onset of labour before caesarean section, rupture of membranes before caesarean section, known fetal anomalies, known maternal collagen vascular disease, maternal diabetes mellitus, lactose intolerance, and maternal age younger than 18 years
Interventions	Supplement group of 10 women received a standard prenatal vitamin (containing 120 mg of vitamin C and 30 IU of vitamin E) plus (400 IU of vitamin E and 500 mg of vitamin C) Control group of 10 women received a standard daily prenatal vitamin (containing 120 mg of vitamin C and 30 IU of vitamin E) Commercially obtained 200-IU vitamin E capsules were enclosed in opaque gelatin capsules by the research pharmacy. The placebos of vitamin E consisted of identical opaque capsules enclosing lactose-containing capsules of identical weight Powdered vitamin C (250 mg) capsules and matched lactose capsules were also prepared by the research pharmacy All patients were instructed to take 1 vitamin E/placebo capsule and 1 vitamin C/placebo capsule twice a day in addition to their regular prenatal vitamin. Compliance was assessed by pill counting at delivery
Outcomes	Concentrations of: 1. Maternal plasma vitamin E 2. Maternal RBC vitamin E 3. Maternal plasma vitamin C 4. Cord plasma vitamin E 5. Cord RBC vitamin E 6. Cord plasma vitamin C 7. Chorioamnion vitamin E 8. Amniotic fluid vitamin C
Notes	This trial did not report any clinical outcomes of interest to the review, and therefore does not contribute any data to the meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Computerised randomisation was performed in blocks of 4.
Allocation concealment (selection bias)	Low risk	Randomisation was done by the research pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded to the supplementation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded to the supplementation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 women from the control group did not complete the protocol because of preterm labour and delivery and samples from her delivery were not available for analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available.
Other bias	Low risk	The baseline is comparable between groups.

Rivas 2000

Methods	Treatment allocation: unclear, women were "randomly divided into two sub-groups" Blinding of outcome assessment: "triple blind" stated. Documentation of exclusion: none stated. Use of placebo control: placebo control.
Participants	127 women were recruited into the study. Inclusion criteria: women less than 29 weeks' gestation and with "high risk for pre-eclampsia", including any of the following factors: nulliparity, previous pre-eclampsia, obesity, hypertension, less than 20 years old, diabetes, nephropathy, mean arterial pressure above of 85 mmHg, positive roll-over test, black race, family history of hypertension or pre-eclampsia, twin pregnancy and poor socioeconomic conditions. Exclusion criteria: unclear, none stated. 127 women were allocated to vitamins C and E, aspirin and fish oil (n = 63) or placebo (n = 64)
Interventions	Women allocated to the treatment group received 400 IU vitamin E per day, 500 mg vitamin C per day, 100 mg aspirin 3 times a week and 1 g fish oil 3 times a day. Women allocated to the placebo group, received placebo "at the same posology and presentation"
Outcomes	1. Pre-eclampsia (not defined) 2. The authors report that "no serious maternal and neonatal side effects of treatment occurred in either group", no other details were given

Notes	Dosage: daily 400 IU vitamin E, above RDI.
	GA at trial entry: unclear, "less than 29 weeks".
	Dietary vitamin E intake before trial entry: unclear, no dietary information reported
	Type of supplement: vitamin E in addition to vitamin C, aspirin and fish oil
	Women's risk status: women were at "high risk for pre-eclampsia"
	Intention-to-treat analyses: unclear, no details given.
	Sample size calculation: unclear, reported as an abstract only
	Compliance: no details given.
	Location: Merida, Venezuela.
	Timeframe: unclear, no details given.
	Published in abstract format only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "prospective, multicentric, randomised, triple-blind, placebo-controlled clinical trial" stated, but no other details provided (only abstract available)
Allocation concealment (selection bias)	Unclear risk	Quote: "prospective, multicentric, randomised, triple-blind, placebo-controlled clinical trial" stated, but no other details provided (only abstract available), no details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Abstract states that the study was "triple blind" and used a placebo control, but no further details provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Abstract states that the study was "triple blind" and used a placebo control, but no further details provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to assess attrition bias.
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	Unclear risk	Insufficient information to assess the potential for other sources of bias

Roberts 2010

Methods	Randomised, double-blind trial was conducted from July 2003 through February 2008 at the 16 clinical centres and the independent data co-ordinating centre of the MFMU Network (USA)
Participants	10,154 pregnant women at 6 clinical centres who had a singleton fetus with a GA of less than 16 weeks 0 days at the time of screening, or who had not had a previous pregnancy that lasted beyond 19 weeks 6 days. Their GA at randomisation was between 9 weeks 0 days and 16 weeks 6 days. Eligible women who were no more than 15 weeks pregnant and who consented to participate in the study were given a supply of placebo and asked to return within 2 weeks
Interventions	Women were to take daily supplementation with 1000 mg of vitamin C and 400 IU of vitamin E between 9th and 16th weeks of pregnancy or matching placebo (mineral oil) Women were instructed to take the study drug each day until they delivered their babies. The study participants returned on a monthly basis to return any unused study drug from the previous month, receive a new supply of the study drug for the coming month, report on side effects, and have their blood pressure and urine protein level (as assessed on dipstick testing) measured
Outcomes	**Primary outcomes** 1. Severe pregnancy-associated hypertension alone 2. Severe or mild hypertension with: elevated liver-enzyme levels, thrombocytopenia, elevated serum creatinine levels, eclamptic seizure, indicated preterm birth, fetal-growth restriction, or perinatal death **Secondary outcomes** were other maternal and neonatal outcomes. 1. Mild pre-eclampsia 2. Severe pre-eclampsia 3. Proteinuria 4. Pulmonary edema 5. Thrombocytopenia 6. HELLP syndrome 7. Preterm birth 8. Fetal or neonatal death 9. SGA 10. Birth weight < 2500 g 11. Admission to NICU 12. RDS
Notes	ClinicalTrials.gov number, NCT00135707.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The simple urn method, with stratification according to clinical centre, was used by the data coordinating centre to create a randomization sequence"

Allocation concealment (selection bias)	Low risk	Boxes containing medications were packaged according to the randomisation sequence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the participants nor the investigators were aware of the treatment assignments" and matching placebo tables used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "identified medical charts of all women with pregnancy-associated hypertension were reviewed centrally by at least 3 reviewers who were unaware of the treatment assignments" and all data was "managed by an independent data coordinating centre"
Incomplete outcome data (attrition bias) All outcomes	Low risk	183 (1.8%) participants were lost to follow-up, 94 in vitamin group and 89 in control group. A further 2 patients (one in each group) had information removed either at their request or by an institutional review board
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes have been reported. (ClinicalTrials.gov number, NCT00135707)
Other bias	Low risk	Baseline characteristics were similar between the 2 groups.

Rumbold 2006

Methods	A multicentre, randomised trial was conducted involving nulliparous women with a singleton pregnancy between 14 and 22 weeks of gestation. The protocol approved by the research and ethics committees at the 9 collaborating hospitals and all women provided written informed consent
Participants	1877 nulliparous women with a singleton pregnancy between 14 and 22 weeks of gestation. Eligible women had normal blood pressure at the first measurement in pregnancy and again at trial entry Women with any of the following were ineligible: known multiple pregnancy, known potentially lethal fetal anomaly, known thrombophilia, chronic renal failure, antihypertensive therapy, or specific contraindications to vitamin C or E therapy such as haemochromatosis or anticoagulant therapy Women were advised not to take any other supplements although a multivitamin that provided a daily intake of no more than 200 mg vitamin C or 50 IU vitamin was permitted

Interventions	Women assigned to the vitamin group were advised to take 4 coated tablets of a combination of 250 mg of vitamin C (as ascorbic acid) and 100 IU of vitamin E (as d-alpha-tocopherol succinate) each day from trial entry until they gave birth. The total daily dose of vitamin C was 1000 mg, and that of vitamin E, 400 IU. Women assigned to placebo were advised to take 4 tablets daily containing microcrystalline cellulose, which were similarly coated and identical in appearance to the vitamin tablets Women were asked to swallow the tablets whole without crushing or chewing them and were advised to take 2 tablets in the morning and 2 tablets in the evening. They were advised not to take any other antioxidant supplements, although a multivitamin preparation that provided a daily intake of no more than 200 mg of vitamin C or 50 IU of vitamin E was permitted. All infants in the study were recommended to receive IM vitamin K after birth
Outcomes	**Primary outcomes** 1. Pre-eclampsia 2. A composite measure of death or serious outcomes in the infant 3. Small for gestational age **Secondary outcomes** *Infants* Serious complications occurring before hospital discharge *Women* A composite of any of the following until 6 weeks postpartum: death, pulmonary oedema, eclampsia, stroke, thrombocytopenia, renal insufficiency, RDS, cardiac arrest, respiratory arrest, placental abruption, abnormal liver function, preterm PROM , major postpartum haemorrhage, postpartum pyrexia, pneumonia, deep-vein thrombosis, or pulmonary embolus requiring anticoagulant therapy **Other secondary outcomes** Antenatal, intrapartum, and postnatal end points, the need for antenatal hospitalisation, antenatal care during the day for hypertension, need for induction of labour for hypertension, use of antihypertensive agents, and use of magnesium sulphate
Notes	The Australian Collaborative Trial of Supplements (ACTS). Location: Australia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule used balanced variable blocks, with stratification by collaborating centre and GA. The schedule was prepared by an investigator not involved in group allocation
Allocation concealment (selection bias)	Low risk	Quote: "The treatment packs contained four sealed, opaque, white plastic bottles of either the antioxidants vitamin C and vitamin E or the placebo and were prepared by a researcher not involved in recruitment or

		clinical care". Randomisation was undertaken using a central telephone service
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, caregivers and researchers were blinded to group allocation until after completion of the study and matching placebo tables were used in the control group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above, the treatment allocations were revealed after the analyses were completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	Baseline characteristics were similar between groups.

Sawhney 2000

Methods	60 women with pre-eclampsia were included in the study and were randomly allocated to treatment (study) and no treatment (control) group
Participants	60 pregnant women with pre-eclampsia participated in the study on the effect of vitamin E supplementation on lipid peroxide levels in pre-eclampsia
Interventions	Vitamin E supplementation versus no treatment.
Outcomes	Lipid peroxide levels were measured by MDA-TBAR assay and alpha-tocopherol levels were measured by HPLC
Notes	Only conference abstract available. No data incorporated in the analysis of this review Setting: India.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The participants were randomly allocated to treatment (study) and no treatment (control) group. No detail was provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned.

Sawhney 2000   *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of pregnant women in each comparison group was not mentioned
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Other bias	Unclear risk	Insufficient information to assess the potential for other sources of bias

Shahraki 2006

Methods	Quasi-randomised trial. Sampling was randomised non presumptive and minimum volume of sample according to minimum volume of sample needed for biological studies (cross-sectional interventional study) A 3-arm comparison and have no control group.
Participants	120 multiparous pregnant women age between 25 to 35 years old being in 25th-28th weeks of pregnancy suffering from leg cramps with normal pregnancy pattern, absence of twin pregnancy, over weight gain and homodynamic background disease, unused medications causing cramp, patients satisfaction conditions of exit from the study were including at the gynaecologic clinic in Shahrekord between September 2004 and July 2005
Interventions	A form containing demographic information. age of pregnancy, number severity and duration of muscular cramps were registered for each women and then a written prescription was given to each of them in order to provide and take the prescription **First group** was given 100 mg vitamin E oral pill a day. **Second group** was given 8 cc milk of magnesium suspension 8%, oral 3 times a day before meal **Third group** was given a 500 mg calcium carbonate oral pill a day. The duration of intervention was 45 days and after 45 days, the women were visited again and information about the number, severity and duration of cramps was registered in the form After 90 days from beginning the treatment, women were visited again and some information about cramps was gathered and registered
Outcomes	1. Number of cramps during each 24 hours 2. Cramp pain duration 3. Cramp severity on a scale of 1-10 (1-5 as low pain rate, 6-10 as high pain rate)

Shahraki 2006 (*Continued*)

Notes	Location: Iran. (Paper was presented with inadequate English proficiency.)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomised trial with unclear details; however, women appeared to be randomised based on the day or time of presentation to the clinic
Allocation concealment (selection bias)	High risk	Quasi-randomised, details are unclear, however women appeared to be randomised based on the day or time of presentation to the clinic
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided about outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total of 120 women with 40 in each arm. First group 4 (3.3%), second group 7 (5. 8%), and third group 7 (5.8%) lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Study protocol was not available.
Other bias	Unclear risk	No details provided about baseline characteristics of treatment groups

Spinnato 2007

Methods	A placebo-controlled, double-blind trial was conducted within the National Institute of Child Health and Human Development (NICHD) Global Network for Women's and Children's Health Research
Participants	Women seeking prenatal care who were $12^{(0/7)}$ to $19^{(6/7)}$ weeks pregnant and diagnosed with non-proteinuric chronic hypertension or a prior history of pre-eclampsia in their most recent pregnancy that progressed beyond 20 weeks' gestation from 4 clinical centre (serves a primarily urban low-income population) at different sites

Interventions	739 women were assigned randomly to receive daily vitamin C 1000 mg and vitamin E 400 IU or placebo. The medications were manufactured as soft gel capsules and each active treatment gel cap contained 500 mg of ascorbic acid, 100 IU of d-alpha tocopherol, 100 IU of d-alpha tocopherol acetate, and excipients (gelatin, soybean oil, glycerin, water lecithin, and caramel colour). The placebo gel caps contained excipients only and were externally identical to the active drug. Participants were instructed to ingest 2 gel caps daily from enrolment until delivery or until the diagnosis of pre-eclampsia. Compliance with treatment was assessed by counting residual pills at monthly return visits. A TrackCap recording was used to motivate optimal compliance and the percentage of women judged by returned pill counts as having received at least 80% of the intended doses was substantial
Outcomes	**Primary outcome** The development of pre-eclampsia **Planned secondary outcomes** Preterm and term PROM **Additional secondary outcomes** 1. Abruptio placentae 2. Preterm birth 3. SGA 4. LBW infants
Notes	Denominators for some outcomes vary due to missing responses, and some vary between publications which separately report outcomes for pre-eclampsia, PROM and chronic hypertension Setting: Brazil.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was constructed by the data coordinating centre as permuted blocks of random size, stratified by clinical centre"
Allocation concealment (selection bias)	Low risk	Quote: Randomisation was "implemented via a program residing on the clinical centre's study computer". "Correct supplier randomization assignment was verified by the data coordinating centre"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All women, caregivers and clinical investigators were blinded, and matching placebo tablets were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical investigators who assessed the data were blinded.

Spinnato 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	32 (4.3%) participants lost to follow-up, 16 in each group. Number of participants were similar between groups and reasons for missing data were described
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes have been reported.
Other bias	Low risk	Baseline characteristics similar between groups.

Villar 2009

Methods	A multicentre, randomised, placebo-controlled, double-blinded trial was performed between October 2004 and December 2006, at antenatal clinics that served populations with low socioeconomic status and had evidence of overall low nutritional status from a previous WHO survey. These clinics, located in Nagpur, India; Lima and Trujillo, Peru; Cape Town, South Africa; and Ho Chi Minh City, Viet Nam form part of the WHO Maternal and Perinatal Research Network--all having extensive experience in conducting large multicentre randomised trials. The trial followed the research protocol used in the recently completed United Kingdom based multicentre trial of vitamins C and E (the VIP trial) 5 with only minor adaptations to accommodate local resources
Participants	1365 pregnant women between14-22 GA with high risk for pre-eclampsia (chronic hypertension, renal disease, pre-eclampsia-eclampsia in the pregnancy preceding the index pregnancy requiring delivery before 37 weeks' gestation, HELLP syndrome in any previous pregnancy, pregestational diabetes, primiparous with a BMI $\geq 30 \text{ kg/m}^2$, history of medically indicated preterm delivery, abnormal uterine artery Doppler waveforms and women with antiphospholipid syndrome) were considered eligible Exclusion criteria: women ingesting vitamin supplements that contained ≥ 200 mg of vitamin C and/or ≥ 50 IU of vitamin E and women receiving warfarin
Interventions	Women were assigned randomly to receive vitamin C and E tablets or identical placebos from enrolment (between14-22 GA to delivery), the assigned prescription continued even after pre-eclampsia or hypertension was diagnosed. They were instructed to take 1 tablet and 1 capsule daily and to leave unused tablets or capsules in the blister and to return the blisters at the subsequent trial visit, regardless of whether all tablets and capsules had been taken. The active and placebo tablets for each vitamin were identical in form, colour and taste and were provided in boxes containing 4 blister packs, each marked Monday to Sunday. Custom Pharmaceuticals prepared vitamin C (1000 mg) and identical placebo tablets (microcrystalline cellulose) with addition of tartaric and citric acid to provide similar acidic taste and Banner Pharmacaps prepared identical gelatin capsules containing 400 IU natural source vitamin E (RRR-a-tocopherol) or a placebo (sunflower seed oil) and the tablets and capsules sealed in blister strips, each with a 1-week supply were packaged. For compliance: median compliance was 87%, and was similar between the treatment groups

Outcomes	**Primary outcomes**
	1. Pre-eclampsia
	2. Gestational hypertension
	3. Proteinuria
	4. Severe gestational hypertension
	5. Severe pre-eclampsia
	6. Pre-eclampsia and eclampsia
	7. LBW (< 2500 g)
	8. SGA (< 10th centile of the WHO recommended standard)
	9. Intrauterine or neonatal death before hospital discharge
	Secondary outcomes
	1. Placental abruption
	2. Pre-eclampsia
	3. eclampsia
	4. Preterm delivery (< 37 weeks)
	5. Early preterm delivery (< 34 weeks)
	6. Very LBW (< 1500 g)
	7. ≥ 7 days in the NICU
	8. Congenital malformations.
	Pre-eclampsia information was unavailable for 14 women in the vitamins and 9 in the placebo group. There were data from 81 supplemented (11.8%) and 100 placebo-treated (14.7%) women with multiple pregnancies, for whom newborn outcomes were considered separately
Notes	Women ingesting medications with aspirin-like compounds were not excluded
	Intention-to-treat analyses performed.
	Location: antenatal clinics in India, Peru, South Africa and Viet Nam
	Reported that "Adverse event rates were 4.9 and 4.3% in the vitamins and placebo groups respectively", no further details given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation sequence was blocked by centre in groups of two to ten individuals"
Allocation concealment (selection bias)	Low risk	Central allocation, quote: "randomisation was performed by the statisticians of the British VIP Trial"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators and local research staff were blinded to the allocation, until all analyses were completed. Quote: "The active and placebo tablets for each vitamin were identical in form, colour and taste and were provided in boxes containing four blister packs"

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators and local research staff were blinded to the allocation, until all analyses were completed. Quote: "The active and placebo tablets for each vitamin were identical in form, colour and taste and were provided in boxes containing four blister packs"
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were small losses to follow-up , but the number and reasons were similar across the treatment groups. Quote: "Pre-eclampsia information was unavailable for 14 women (2%) in the vitamins and 9 (1. 3%) in the placebo group, but the remainder of the data from these women was included in the analyses"
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported except neonatal death but perinatal death was reported instead; therefore, there is a low chance of reporting bias
Other bias	Low risk	Baseline characteristics were similar between the groups.

Xu 2010

Methods	A double-blinded, multicentre trial in Canada (17 centres) and Mexico (10 centres) was conducted from January 2004 through March 2006. Randomisation was performed through an electronic data management platform, which enabled randomisation and data entry over the Internet through a secured and restricted-access web site and stored the data in a centralised database
Participants	Women were eligible for the trial if they were between 12 and 18 completed weeks of pregnancy on the basis of last menstrual period and confirmed by early ultrasound examination
Interventions	Women were provided either with the vitamins C and E or placebo with the total daily dose of vitamin C was 1000 mg, and that of vitamin E was 400 IU Women assigned to the vitamin group were advised to take 2 soft gel capsules, each containing 500 mg of vitamin C (ascorbic acid) and 200 IU of vitamin E (100 IU d-alpha-tocopherol, 100 IU d-alpha-tocopheryl acetate). Women in the placebo group were advised to take capsules that were identical in appearance to the active treatment capsules. Women were asked to swallow the capsules whole without crushing or chewing them and were advised not to take other antioxidant supplements. At the time of randomisation and at 26 weeks of gestation, participants compliance was calculated as the proportion of tablets not returned in the bottles over the total number of tablets given to each woman

	and defined as compliant to treatment if > 80% of tablets were used
Outcomes	**Primary outcomes** 1. Gestational hypertension 2. Adverse conditions: diastolic pressure or systolic pressure; proteinuria; eclampsia; thrombocytopenia; elevated liver enzyme levels; haematocrit or blood transfusion; IUGR birthweight < 3rd centile for GA; and perinatal death (fetal death > 20 weeks or neonatal death within 7 days)
Notes	They planned to recruit 5000 women per group in stratum I (low risk) for a total of 10,000 women and 1250 women per group in stratum II (high risk) for a total of 2500 women to detect 30% reduction of pre-eclampsia, with a power of 90% and alpha error of 5%. The trial was prematurely stopped with a total of 2640 eligible pregnant women included in the final analysis due to adverse outcome Location: Canada and Mexico.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation performed through an electronic data management platform", with stratification for centre and maternal risk status
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation performed through an electronic data management platform", with stratification for centre and maternal risk status
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women, trial staff and caregivers were blinded to the treatment allocation until the analyses had been completed. In additional matching placebo tablets were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women, trial staff and caregivers were blinded to the treatment allocation until the analyses had been completed. In additional matching placebo tablets were used
Incomplete outcome data (attrition bias) All outcomes	Low risk	277 (10.5%) women lost to follow-up, 148 (11%) in the vitamin group and 129 (10%) in the placebo groups, therefore, the proportion of missing data was similar across treatment groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.

Other bias	Unclear risk	Baseline characteristics were similar across groups, however, the trial was terminated early once the results of Poston 2006 and Rumbold 2005 were published. A total of 2640 participants were assessed (planned to recruit 10,000)

BMI: body mass index
DIC: disseminated intravascular coagulation
GA: gestational age
HELLP: haemolysis, elevated liver enzymes, low platelets
HPLC: high performance liquid chromatography
IM: intramuscular
IQR: interquartile range
IU: international units
IUGR: Intrauterine growth retardation
IVH: intraventricular haemorrhage
LBW: low birthweight
MDA-TBAR: malondialdehyde-thiobarbituric acid reactive
NEC: necrotising enterocolitis
NICU: neonatal intensive care unit
NSAID: non-steroidal anti-inflammatories
PAI-1: plasminogen activator inhibitor-1
PAI-2: plasminogen activator inhibitor-2
PROM: prelabour rupture of membranes
RDI: recommended dietary intake
RDS: respiratory distress syndrome
SD: standard deviation
SGA: small-for-gestational age
WHO: World Health Organization

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

Study	Reason for exclusion
Bolisetty 2002	Not a randomised trial, pilot case-control study. 12 women at risk of preterm birth and between 30 and 36 weeks' gestation were given daily 20 mg beta-carotene, 167.8 mg vitamin E and 1000 mg vitamin C or acted as controls. Biochemical assessments of oxidative stress and maternal plasma concentrations of beta-carotene, vitamin E and vitamin C were reported
Clark 2012	The intervention was dietary advice to optimise vitamin E intake to 15 mg/day, not specifically vitamin E supplementation

(Continued)

Lietz 2001	Not a randomised trial. Women were supplemented with either red palm oil (a source of vitamin A), sunflower oil (a source of vitamin E) or acted as control. Allocation to treatment groups was "based on practicality". Reported outcomes included measures of plasma and breast milk vitamin A status, maternal haemoglobin and maternal weight
Moldenhauer 2002	Women were not randomised to vitamin E supplementation. Women in this study were participating in a randomised placebo-controlled trial of calcium supplementation, and completed a dietary assessment at 12 to 21 weeks' gestation and 29 to 31 weeks' gestation. Unclear whether all women took a standard prenatal multivitamin or just women in the placebo group. Results are presented according to "teens", "twins" and "singleton" pregnancies, not according to whether women took the supplement or not. Outcomes reported included dietary intakes of vitamin C and E (with and without the contribution of the prenatal vitamin supplement). Published in abstract form only
Wibowo 2012	The Intervention was a multivitamin supplement including vitamin E, more than 14 other vitamins were also included in the supplement

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

Tan 1997

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unable to trace full paper.

D A T A   A N D   A N A L Y S E S

Comparison 1.   Any vitamin E supplementation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stillbirth	9	19023	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.88, 1.56]
2 Neonatal death	9	18617	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.13]
3 Perinatal death	6	16923	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.77, 1.54]
4 Infant death	1	2694	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [0.12, 74.12]
5 Haemolytic anemia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Reticulocytosis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Hyperbilirubinemia	1	725	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.59, 1.04]
8 Haemoglobin levels	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.1 Maternal	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Infant	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Preterm birth (less than 37 weeks' gestation)	11	20565	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
10 Clinical pre-eclampsia (random-effects model)	14	20878	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.06]
11 Intrauterine growth restriction (various definitions)	11	20202	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]
11.1 Birthweight < 10th centile	8	10161	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.90, 1.06]
11.2 IUGR definition unclear	1	216	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.45, 1.97]
11.3 Birthweight < 1 SD for gestational age	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.28, 8.12]
11.4 Birthweight < 3rd centile	1	9781	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.79, 1.27]
12 Birthweight	10	16888	Mean Difference (IV, Random, 95% CI)	22.17 [-23.01, 67.36]
13 Prelabour rupture of fetal membranes	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Preterm	5	1999	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.93, 1.75]
13.2 Term	2	2504	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.37, 2.28]
14 Maternal death	7	17120	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.14, 2.51]
15 Elective delivery and caesarean section	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Prelabour caesarean section	2	1932	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.85, 1.56]
15.2 Any caesarean section	6	15297	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.97, 1.07]
15.3 Induction of labour	1	1877	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.97, 1.26]
16 Bleeding episodes	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Placental abruption	7	14922	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.44, 0.93]
16.2 Antepartum haemorrhage	2	12256	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.85, 1.82]
17 Measures of serious maternal morbidity	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Eclampsia	8	19471	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.82, 3.41]

17.2 Renal failure or insufficiency	2	1933	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.55, 4.02]
17.3 Disseminated intravascular coagulation	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.41]
17.4 Pulmonary oedema	4	12569	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.16, 1.03]
18 Peripheral neuropathy	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.1 Maternal	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Infant	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Maternal satisfaction with care	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Gestational age at birth	7	13783	Mean Difference (IV, Random, 95% CI)	0.15 [-0.12, 0.43]
21 Congenital malformations	4	5511	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.83, 1.63]
22 Apgar score less than seven at five minutes	3	3531	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.42, 1.27]
23 Vitamin K deficiency bleeding or haemorrhagic disease of the newborn	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Respiratory distress syndrome	8	18574	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.08]
25 Chronic lung disease or bronchopulmonary dysplasia	3	3262	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.10, 4.69]
26 Periventricular haemorrhage and periventricular leukomalacia	6	17787	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.58, 1.42]
27 Bacterial sepsis	5	13324	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.73, 1.67]
28 Necrotising enterocolitis	7	18514	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.36, 1.55]
29 Retinopathy of prematurity	6	18270	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.72, 1.93]
30 Disability at childhood follow-up	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 Poor childhood growth	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32 Adverse events related to vitamin E supplementation	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33 Side effects of vitamin E supplementation	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 Acne	1	56	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.14, 75.68]
33.2 Transient weakness	1	56	Risk Ratio (M-H, Fixed, 95% CI)	5.36 [0.27, 106.78]
33.3 Skin rash	1	56	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.14, 75.68]
33.4 Any side effects (symptoms not reported separately by group status)	1	707	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.39, 3.41]
33.5 Abdominal pain	1	1877	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.16, 2.37]
33.6 Elevated liver enzymes (defined by authors)	3	14209	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.71, 1.41]
34 Use of health service resources - maternal	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
34.1 Admission to intensive care unit	2	3718	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.16, 2.30]
34.2 Hospitalisations in pregnancy	2	2407	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.30, 1.80]
35 Use of health service resources - infant	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 Admission to intensive care unit	8	17594	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.2 Use of mechanical ventilation	6	8531	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.84, 1.25]

Comparison 2. Any vitamin E supplementation (sensitivity analyses by trial quality)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stillbirth	8	18777	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.89, 1.58]
1.1 Low overall risk of bias	8	18777	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.89, 1.58]
2 Neonatal death	7	18314	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.57, 1.24]
2.1 Low overall risk of bias	7	18314	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.57, 1.24]
3 Perinatal death	5	16677	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.82, 1.73]
3.1 Low overall risk of bias	5	16677	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.82, 1.73]
4 Preterm birth (< 37 weeks' gestation)	8	20205	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.07]
4.1 Low overall risk of bias	8	20205	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.07]
5 Clinical pre-eclampsia	8	19698	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.10]
5.1 Low overall risk of bias	8	19698	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.10]
6 Intrauterine growth restriction	8	19842	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]
6.1 Low overall risk of bias	8	19842	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]

Comparison 3. Any vitamin E supplementation (subgroup analyses based on gestation at entry)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stillbirth	9	19023	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.88, 1.56]
1.1 Less than or equal to 20 week's gestation	3	13084	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.73, 1.55]
1.2 Greater than 20 weeks' gestation	2	302	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.35, 1.70]
1.3 Both prior to and after 20 weeks' gestation	4	5637	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.96, 2.70]
2 Neonatal death	9	18617	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.13]
2.1 Less than or equal to 20 weeks' gestation	3	12977	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.53, 1.39]
2.2 Greater than 20 weeks' gestation	3	343	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.51, 1.68]
2.3 Both prior to and after 20 weeks' gestation	3	5297	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.28, 1.22]
3 Perinatal death	6	16923	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.77, 1.54]
3.1 Less than or equal to 20 weeks' gestation	2	12332	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.42, 6.87]
3.2 Greater than 20 weeks' gestation	2	302	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.49, 1.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Both prior to and after 20 weeks' gestation	2	4289	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.60, 2.14]
4 Preterm birth	11	20565	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
4.1 Less than or equal to 20 weeks' gestation	5	13465	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.20]
4.2 Greater than 20 weeks' gestation	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Both prior to and after 20 weeks' gestation	6	7100	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.10]
5 Clinical pre-eclampsia	14	20878	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.06]
5.1 Less than or equal to 20 weeks' gestation	5	13299	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.16]
5.2 Greater than 20 weeks' gestation	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Both prior to and after 20 weeks' gestation	7	6886	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.73, 1.12]
5.4 Gestation at trial entry unknown	2	693	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.13, 0.79]
6 Intrauterine growth restriction	11	20202	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]
6.1 Less than or equal to 20 week's gestation	5	13285	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.10]
6.2 Greater than 20 weeks' gestation	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Both prior to and after 20 weeks' gestation	6	6917	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.08]

Comparison 4. Any vitamin E supplementation (subgroup analyses by dietary intake)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stillbirth	9	19023	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.88, 1.56]
1.1 Low dietary intake	1	1867	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.47, 3.84]
1.2 Adequate dietary intake	1	9855	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.67, 1.66]
1.3 Dietary intake unclear	7	7301	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.85, 1.84]
2 Neonatal death	9	18617	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.13]
2.1 Low dietary intake	1	1853	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.24]
2.2 Adequate dietary intake	1	9781	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.41, 1.31]
2.3 Dietary intake unclear	7	6983	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.60, 1.37]
3 Perinatal death	6	16923	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.77, 1.54]
3.1 "Low nutritional status"	1	1515	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.59, 1.17]
3.2 Adequate dietary intake	1	9969	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.48, 2.46]
3.3 Dietary intake unclear	4	5439	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.75, 2.11]
4 Preterm birth (less than 37 weeks' gestation)	11	20565	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
4.1 "Low nutritional status"	1	1343	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.03]
4.2 Low dietary intake	1	1877	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.73, 1.43]
4.3 Adequate dietary intake	1	9969	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.09]
4.4 Dietary intake unclear	8	7376	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.83, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Clinical pre-eclampsia (random-effects model)	14	20796	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.03]
5.1 "Low nutritional status"	1	1355	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]
5.2 Low baseline vitamin E status (≤ 5 µmol/mmol cholesterol)	1	95	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.12, 1.02]
5.3 Moderate/high baseline antioxidant status (> 5 µmol/ mmol cholesterol)	1	572	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.53, 1.12]
5.4 Low dietary intake	1	1877	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.82, 1.75]
5.5 Adequate dietary intake	1	9969	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.93, 1.24]
5.6 Dietary intake unclear	10	6928	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.56, 0.98]
6 Intrauterine growth restriction (less than third centile or the most extreme centile reported)	11	20202	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]
6.1 "Low nutritional status"	1	1165	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.12]
6.2 Low dietary intake	1	1853	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.66, 1.16]
6.3 Adequate dietary intake	1	9781	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.79, 1.27]
6.4 Dietary intake unclear	8	7403	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.10]

Comparison 5.   Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stillbirth	9	19023	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.88, 1.56]
1.1 High/increased risk	7	7301	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.85, 1.84]
1.2 Low/moderate risk	2	11722	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.72, 1.66]
2 Neonatal death	9	18617	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.13]
2.1 High/increased risk	7	6983	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.60, 1.37]
2.2 Low/moderate risk	2	11634	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.39, 1.17]
3 Perinatal death	6	16923	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.77, 1.54]
3.1 High/increased risk	5	6954	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.73, 1.67]
3.2 Low/moderate risk	1	9969	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.48, 2.46]
4 Preterm birth (less than 37 weeks' gestation)	11	20565	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
4.1 High/increased risk	8	8503	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.13]
4.2 Low/moderate risk	3	12062	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.23]
5 Clinical pre-eclampsia (random-effects model)	14	20878	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.06]
5.1 High/increased risk	9	8123	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.06]
5.2 Low/moderate risk	5	12755	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.56, 1.27]
6 Intrauterine growth restriction (less than third centile or the most extreme centile reported)	11	20202	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]
6.1 High/increased risk	8	8352	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.08]
6.2 Low/moderate risk	3	11850	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]

Analysis 1.1.   Comparison 1 Any vitamin E supplementation, Outcome 1 Stillbirth.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 1 Stillbirth

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chappell 1999	1/141	2/142		2.3 %	0.50 [0.05, 5.49]
Gulmezoglu 1997	7/27	9/29		10.1 %	0.84 [0.36, 1.93]
Gungorduk 2014	1/125	2/121		2.4 %	0.48 [0.04, 5.27]
McCance 2010	9/373	8/373		9.3 %	1.13 [0.44, 2.88]
Poston 2006	19/1369	7/1372		8.2 %	2.72 [1.15, 6.45]
Roberts 2010	38/4938	36/4917		42.1 %	1.05 [0.67, 1.66]
Rumbold 2006	8/932	6/935		7.0 %	1.34 [0.47, 3.84]
Spinnato 2007	7/351	10/349		11.7 %	0.70 [0.27, 1.81]
Xu 2010	10/1237	6/1292		6.9 %	1.74 [0.63, 4.78]
Total (95% CI)	**9493**	**9530**		**100.0 %**	**1.17 [0.88, 1.56]**

Total events: 100 (Vitamin E), 86 (Control)

Heterogeneity: Chi^2 = 7.31, df = 8 (P = 0.50); I^2 =0.0%

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

```
         0.01    0.1     1      10    100
      Favours vitamin E     Favours control
```

Analysis 1.2. Comparison 1 Any vitamin E supplementation, Outcome 2 Neonatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 2 Neonatal death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Borna 2005	4/30	5/30		6.6 %	0.80 [0.24, 2.69]
Gulmezoglu 1997	5/20	1/20		1.3 %	5.00 [0.64, 39.06]
Gungorduk 2014	10/124	14/119		19.0 %	0.69 [0.32, 1.48]
McCance 2010	2/364	3/366		4.0 %	0.67 [0.11, 3.99]
Poston 2006	8/1350	12/1364		15.9 %	0.67 [0.28, 1.64]
Roberts 2010	20/4900	27/4881		36.0 %	0.74 [0.41, 1.31]
Rumbold 2006	1/924	4/929		5.3 %	0.25 [0.03, 2.24]
Spinnato 2007	6/344	6/339		8.0 %	0.99 [0.32, 3.03]
Xu 2010	5/1227	3/1286		3.9 %	1.75 [0.42, 7.29]
Total (95% CI)	**9283**	**9334**		**100.0 %**	**0.81 [0.58, 1.13]**

Total events: 61 (Vitamin E), 75 (Control)

Heterogeneity: Chi² = 5.82, df = 8 (P = 0.67); I² =0.0%

Test for overall effect: Z = 1.25 (P = 0.21)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours vitamin E   Favours control

Analysis 1.3. Comparison 1 Any vitamin E supplementation, Outcome 3 Perinatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 3 Perinatal death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Gulmezoglu 1997	12/27	10/29		16.8 %	1.29 [0.67, 2.48]
Gungorduk 2014	11/125	16/121		14.8 %	0.67 [0.32, 1.38]
Poston 2006	43/1383	27/1391		23.5 %	1.60 [1.00, 2.58]
Roberts 2010	12/4993	11/4976		12.6 %	1.09 [0.48, 2.46]
Villar 2009	56/753	68/762		30.0 %	0.83 [0.59, 1.17]
Xu 2010	5/1167	1/1196		2.4 %	5.12 [0.60, 43.79]
Total (95% CI)	**8448**	**8475**		**100.0 %**	**1.09 [0.77, 1.54]**

Total events: 139 (Vitamin E), 133 (Control)

Heterogeneity: Tau² = 0.07; Chi² = 8.82, df = 5 (P = 0.12); I² =43%

Test for overall effect: Z = 0.50 (P = 0.61)

Test for subgroup differences: Not applicable

```
        0.1  0.2   0.5   1    2    5   10
        Favours vitamin E    Favours control
```

Analysis 1.4. Comparison 1 Any vitamin E supplementation, Outcome 4 Infant death.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 4 Infant death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Poston 2006	1/1342	0/1352		100.0 %	3.02 [0.12, 74.12]
Total (95% CI)	**1342**	**1352**		**100.0 %**	**3.02 [0.12, 74.12]**
Total events: 1 (Vitamin E), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control
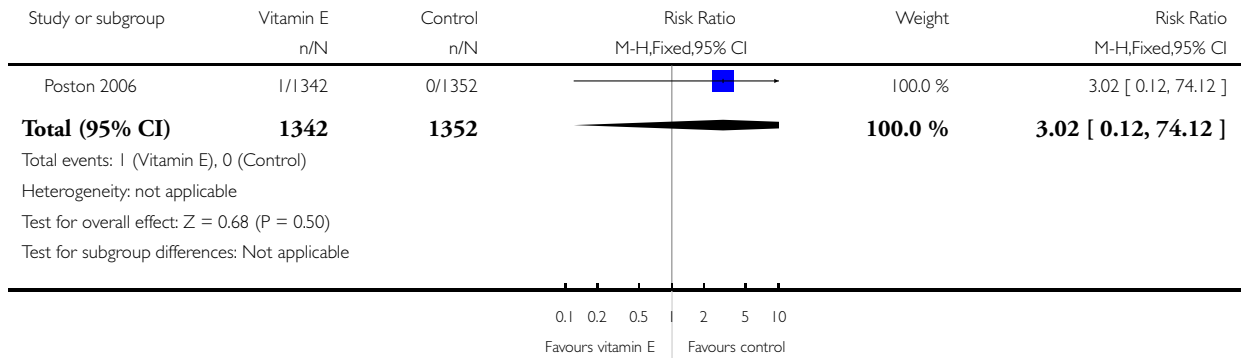
Analysis 1.7. Comparison 1 Any vitamin E supplementation, Outcome 7 Hyperbilirubinemia.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 7 Hyperbilirubinemia

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McCance 2010	68/362	87/363		100.0 %	0.78 [0.59, 1.04]
Total (95% CI)	**362**	**363**		**100.0 %**	**0.78 [0.59, 1.04]**
Total events: 68 (Vitamin E), 87 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.69 (P = 0.090)					
Test for subgroup differences: Not applicable					

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control
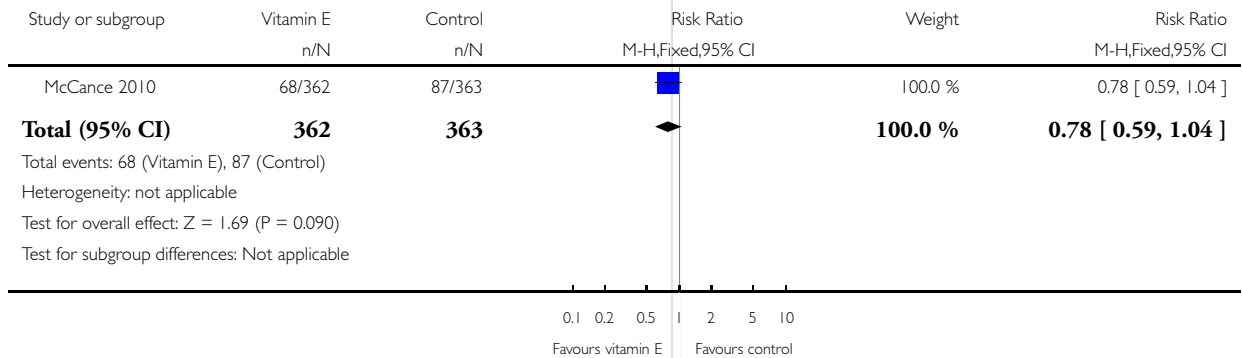
Analysis 1.9. Comparison 1 Any vitamin E supplementation, Outcome 9 Preterm birth (less than 37 weeks' gestation).

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 9 Preterm birth (less than 37 weeks' gestation)

Study or subgroup	Vitamin E	Control	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Beazley 2005	20/52	14/48		3.1 %	1.32 [0.75, 2.31]
Chappell 1999	6/141	5/142		0.8 %	1.21 [0.38, 3.87]
Huria 2010	5/107	16/109		1.1 %	0.32 [0.12, 0.84]
Kalpdev 2011	3/22	10/22		0.8 %	0.30 [0.10, 0.94]
McCance 2010	126/375	152/374		13.3 %	0.83 [0.69, 1.00]
Poston 2006	400/1372	373/1376		17.7 %	1.08 [0.95, 1.21]
Roberts 2010	513/4993	526/4976		18.0 %	0.97 [0.87, 1.09]
Rumbold 2006	64/935	63/942		7.0 %	1.02 [0.73, 1.43]
Spinnato 2007	96/351	82/349		9.9 %	1.16 [0.90, 1.50]
Villar 2009	188/674	213/669		14.8 %	0.88 [0.74, 1.03]
Xu 2010	193/1243	184/1293		13.4 %	1.09 [0.91, 1.31]
Total (95% CI)	**10265**	**10300**		**100.0 %**	**0.98 [0.88, 1.09]**

Total events: 1614 (Vitamin E), 1638 (Control)

Heterogeneity: Tau^2 = 0.01; Chi^2 = 20.80, df = 10 (P = 0.02); I^2 =52%

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control

Analysis 1.10. Comparison 1 Any vitamin E supplementation, Outcome 10 Clinical pre-eclampsia (random-effects model).

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 10 Clinical pre-eclampsia (random-effects model)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Beazley 2005	9/52	9/48		2.7 %	0.92 [0.40, 2.13]
Chappell 1999	11/141	24/142		3.9 %	0.46 [0.24, 0.91]
Huria 2010	5/107	11/109		1.9 %	0.46 [0.17, 1.29]
Kalpdev 2011	2/22	3/22		0.7 %	0.67 [0.12, 3.61]
Mahdy 2004	1/46	2/67		0.4 %	0.73 [0.07, 7.80]
McCance 2010	57/375	70/374		10.6 %	0.81 [0.59, 1.12]
Nasrolahi 2006	5/290	18/290		2.0 %	0.28 [0.10, 0.74]
Poston 2006	181/1196	187/1199		15.6 %	0.97 [0.80, 1.17]
Rivas 2000	1/63	14/64		0.5 %	0.07 [0.01, 0.54]
Roberts 2010	358/4993	332/4976		17.5 %	1.07 [0.93, 1.24]
Rumbold 2006	56/935	47/942		8.8 %	1.20 [0.82, 1.75]
Spinnato 2007	49/355	55/352		9.4 %	0.88 [0.62, 1.26]
Villar 2009	164/681	157/674		15.5 %	1.03 [0.85, 1.25]
Xu 2010	69/1167	68/1196		10.4 %	1.04 [0.75, 1.44]
Total (95% CI)	**10423**	**10455**		**100.0 %**	**0.91 [0.79, 1.06]**

Total events: 968 (Vitamin E), 997 (Control)

Heterogeneity: Tau^2 = 0.03; Chi^2 = 24.90, df = 13 (P = 0.02); I^2 =48%

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: Not applicable

0.001 0.01 0.1 1 10 100 1000

Favours vitamin E   Favours control

Analysis 1.11. Comparison 1 Any vitamin E supplementation, Outcome 11 Intrauterine growth restriction (various definitions).

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 11 Intrauterine growth restriction (various definitions)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Birthweight < 10th centile					
Beazley 2005	2/52	4/48		0.4 %	0.46 [0.09, 2.41]
Chappell 1999	33/141	45/142		4.2 %	0.74 [0.50, 1.08]
McCance 2010	23/373	36/372		3.4 %	0.64 [0.39, 1.05]
Poston 2006	403/1385	360/1386		33.5 %	1.12 [0.99, 1.26]
Rumbold 2006	80/924	92/929		8.5 %	0.87 [0.66, 1.16]
Spinnato 2007	49/356	49/352		4.6 %	0.99 [0.68, 1.43]
Villar 2009	141/592	149/573		14.1 %	0.92 [0.75, 1.12]
Xu 2010	173/1243	194/1293		17.7 %	0.93 [0.77, 1.12]
Subtotal (95% CI)	**5066**	**5095**		**86.3 %**	**0.98 [0.90, 1.06]**
Total events: 904 (Vitamin E), 929 (Control)					
Heterogeneity: Chi^2 = 11.80, df = 7 (P = 0.11); I^2 =41%					
Test for overall effect: Z = 0.59 (P = 0.56)					
2 IUGR definition unclear					
Huria 2010	12/107	13/109		1.2 %	0.94 [0.45, 1.97]
Subtotal (95% CI)	**107**	**109**		**1.2 %**	**0.94 [0.45, 1.97]**
Total events: 12 (Vitamin E), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.16 (P = 0.87)					
3 Birthweight < 1 SD for gestational age					
Kalpdev 2011	3/22	2/22		0.2 %	1.50 [0.28, 8.12]
Subtotal (95% CI)	**22**	**22**		**0.2 %**	**1.50 [0.28, 8.12]**
Total events: 3 (Vitamin E), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					
4 Birthweight < 3rd centile					
Roberts 2010	133/4900	132/4881		12.3 %	1.00 [0.79, 1.27]
Subtotal (95% CI)	**4900**	**4881**		**12.3 %**	**1.00 [0.79, 1.27]**
Total events: 133 (Vitamin E), 132 (Control)					
Heterogeneity: not applicable					

```
          0.01   0.1    1    10   100
        Favours vitamin E    Favours control
```

(*Continued* . . .)

Study or subgroup	Vitamin E	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI

Test for overall effect: Z = 0.03 (P = 0.98)

Total (95% CI)   **10095**   **10107**   **100.0 %**   **0.98 [0.91, 1.06]**

Total events: 1052 (Vitamin E), 1076 (Control)

Heterogeneity: Chi² = 12.06, df = 10 (P = 0.28); I² =17%

Test for overall effect: Z = 0.52 (P = 0.60)

Test for subgroup differences: Chi² = 0.30, df = 3 (P = 0.96), I² =0.0%

```
        0.01   0.1    1    10   100
      Favours vitamin E   Favours control
```

Analysis 1.12. Comparison 1 Any vitamin E supplementation, Outcome 12 Birthweight.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 12 Birthweight

Study or subgroup	Vitamin E		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Beazley 2005	52	2911 (901)	48	3050 (1021)		1.3 %	-139.00 [-517.68, 239.68]
Borna 2005 (1)	30	1978 (890)	30	2221 (78)		1.8 %	-243.00 [-562.70, 76.70]
Gungorduk 2014	125	1859.7 (567.3)	121	1658.1 (623.1)		6.5 %	201.60 [52.55, 350.65]
Kalpdev 2011	22	2710 (600)	22	2450 (530)		1.7 %	260.00 [-74.53, 594.53]
McCance 2010	373	3435 (802)	372	3355 (800)		9.0 %	80.00 [-35.04, 195.04]
Nasrolahi 2006	290	3370 (220)	290	3295 (270)		18.5 %	75.00 [34.92, 115.08]
Poston 2006	1385	2901 (891)	1386	2967 (873)		14.9 %	-66.00 [-131.68, -0.32]
Roberts 2010	4900	3247 (575)	4881	3244 (581)		20.6 %	3.00 [-19.91, 25.91]
Rumbold 2006	924	3392 (599)	929	3386 (584)		16.6 %	6.00 [-47.87, 59.87]
Spinnato 2007	356	3019.7 (779.3)	352	3039.7 (767.5)		9.1 %	-20.00 [-133.94, 93.94]
Total (95% CI)	**8457**		**8431**			**100.0 %**	**22.17 [-23.01, 67.36]**

Heterogeneity: Tau² = 2448.59; Chi² = 28.41, df = 9 (P = 0.00081); I² =68%

Test for overall effect: Z = 0.96 (P = 0.34)

Test for subgroup differences: Not applicable

```
      -1000  -500    0    500   1000
      Favours control   Favours vitamin E
```

(1) The SD for the control group is very small, however this is the figure reported in publication.

Analysis 1.13.   Comparison 1 Any vitamin E supplementation, Outcome 13 Prelabour rupture of fetal membranes.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 13 Prelabour rupture of fetal membranes

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Preterm					
McCance 2010	23/126	31/152		18.6 %	0.90 [0.55, 1.45]
Roberts 2010	124/513	129/526		28.6 %	0.99 [0.80, 1.22]
Rumbold 2006	30/64	23/63		20.9 %	1.28 [0.85, 1.95]
Spinnato 2007	16/96	6/82		9.1 %	2.28 [0.93, 5.55]
Xu 2010	64/193	33/184		22.8 %	1.85 [1.28, 2.67]
Subtotal (95% CI)	**992**	**1007**		**100.0 %**	**1.27 [0.93, 1.75]**

Total events: 257 (Vitamin E), 222 (Control)
Heterogeneity: Tau^2 = 0.08; Chi^2 = 11.91, df = 4 (P = 0.02); I^2 =66%
Test for overall effect: Z = 1.50 (P = 0.13)

2 Term					
Spinnato 2007	37/253	19/266		23.5 %	2.05 [1.21, 3.46]
Xu 2010	109/974	67/1011		76.5 %	1.69 [1.26, 2.26]
Subtotal (95% CI)	**1227**	**1277**		**100.0 %**	**1.77 [1.37, 2.28]**

Total events: 146 (Vitamin E), 86 (Control)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%
Test for overall effect: Z = 4.38 (P = 0.000012)
Test for subgroup differences: Chi^2 = 2.48, df = 1 (P = 0.12), I^2 =60%

```
         0.1  0.2   0.5   1    2    5   10
        Favours vitamin E    Favours control
```

Analysis 1.14. Comparison I Any vitamin E supplementation, Outcome 14 Maternal death.

Review: Vitamin E supplementation in pregnancy

Comparison: I Any vitamin E supplementation

Outcome: I4 Maternal death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gulmezoglu 1997	0/27	0/29			Not estimable
McCance 2010	0/379	1/382		29.9 %	0.34 [0.01, 8.22]
Poston 2006	1/1196	1/1199		20.0 %	1.00 [0.06, 16.01]
Roberts 2010	1/4993	1/4976		20.0 %	1.00 [0.06, 15.93]
Rumbold 2006	0/935	0/942			Not estimable
Spinnato 2007	0/355	0/352			Not estimable
Villar 2009	0/681	1/674		30.1 %	0.33 [0.01, 8.08]
Total (95% CI)	**8566**	**8554**		**100.0 %**	**0.60 [0.14, 2.51]**

Total events: 2 (Vitamin E), 4 (Control)

Heterogeneity: Chi² = 0.52, df = 3 (P = 0.91); I² =0.0%

Test for overall effect: Z = 0.70 (P = 0.48)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 I 2 5 I0

Favours vitamin E   Favours control

Analysis 1.15. Comparison 1 Any vitamin E supplementation, Outcome 15 Elective delivery and caesarean section.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 15 Elective delivery and caesarean section

Study or subgroup	Vitamin e n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Prelabour caesarean section					
Gulmezoglu 1997	16/27	11/28		16.5 %	1.51 [0.86, 2.63]
Rumbold 2006	59/935	55/942		83.5 %	1.08 [0.76, 1.54]
Subtotal (95% CI)	**962**	**970**		**100.0 %**	**1.15 [0.85, 1.56]**
Total events: 75 (Vitamin e), 66 (Control)					
Heterogeneity: Chi² = 1.03, df = 1 (P = 0.31); I² =3%					
Test for overall effect: Z = 0.90 (P = 0.37)					
2 Any caesarean section					
Gungorduk 2014	19/125	24/121		1.1 %	0.77 [0.44, 1.32]
Huria 2010	18/107	23/109		1.0 %	0.80 [0.46, 1.39]
Roberts 2010	1269/4958	1224/4940		54.1 %	1.03 [0.97, 1.11]
Rumbold 2006	250/935	248/942		10.9 %	1.02 [0.87, 1.18]
Spinnato 2007	231/349	236/348		10.4 %	0.98 [0.88, 1.08]
Xu 2010	520/1167	517/1196		22.5 %	1.03 [0.94, 1.13]
Subtotal (95% CI)	**7641**	**7656**		**100.0 %**	**1.02 [0.97, 1.07]**
Total events: 2307 (Vitamin e), 2272 (Control)					
Heterogeneity: Chi² = 2.67, df = 5 (P = 0.75); I² =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
3 Induction of labour					
Rumbold 2006	311/935	283/942		100.0 %	1.11 [0.97, 1.26]
Subtotal (95% CI)	**935**	**942**		**100.0 %**	**1.11 [0.97, 1.26]**
Total events: 311 (Vitamin e), 283 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.50 (P = 0.13)					
Test for subgroup differences: Chi² = 1.82, df = 2 (P = 0.40), I² =0.0%					

```
        0.1   0.2   0.5    1    2    5    10
     Favours vitamin E      Favours control
```

Analysis 1.16. Comparison 1 Any vitamin E supplementation, Outcome 16 Bleeding episodes.

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Placental abruption					
Chappell 1999	1/141	3/142		4.3 %	0.34 [0.04, 3.19]
Gulmezoglu 1997	2/27	6/29		8.3 %	0.36 [0.08, 1.62]
McCance 2010	5/375	7/374		10.0 %	0.71 [0.23, 2.22]
Roberts 2010	24/4957	36/4938		51.6 %	0.66 [0.40, 1.11]
Rumbold 2006	3/935	1/942		1.4 %	3.02 [0.31, 29.00]
Spinnato 2007	4/355	8/352		11.5 %	0.50 [0.15, 1.63]
Villar 2009	6/681	9/674		12.9 %	0.66 [0.24, 1.84]
Subtotal (95% CI)	**7471**	**7451**		**100.0 %**	**0.64 [0.44, 0.93]**
Total events: 45 (Vitamin E), 70 (Control)					
Heterogeneity: Chi² = 2.93, df = 6 (P = 0.82); I² =0.0%					
Test for overall effect: Z = 2.33 (P = 0.020)					
2 Antepartum haemorrhage					
Roberts 2010	56/4956	46/4937		95.9 %	1.21 [0.82, 1.79]
Xu 2010	4/1167	2/1196		4.1 %	2.05 [0.38, 11.17]
Subtotal (95% CI)	**6123**	**6133**		**100.0 %**	**1.25 [0.85, 1.82]**
Total events: 60 (Vitamin E), 48 (Control)					
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Chi² = 5.99, df = 1 (P = 0.01), I² =83%					

```
         0.01   0.1    1    10   100
      Favours vitamin E    Favours control
```

Analysis 1.17. Comparison 1 Any vitamin E supplementation, Outcome 17 Measures of serious maternal morbidity.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 17 Measures of serious maternal morbidity

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Eclampsia					
Gulmezoglu 1997	1/27	1/29		8.0 %	1.07 [0.07, 16.33]
McCance 2010	1/375	2/374		16.7 %	0.50 [0.05, 5.48]
Poston 2006	3/1196	1/1199		8.3 %	3.01 [0.31, 28.87]
Roberts 2010	10/4993	4/4976		33.4 %	2.49 [0.78, 7.94]
Rumbold 2006	0/935	0/942			Not estimable
Spinnato 2007	0/355	1/352		12.6 %	0.33 [0.01, 8.09]
Villar 2009	3/681	2/674		16.8 %	1.48 [0.25, 8.86]
Xu 2010	1/1167	0/1196		4.1 %	3.07 [0.13, 75.39]
Subtotal (95% CI)	**9729**	**9742**		**100.0 %**	**1.67 [0.82, 3.41]**
Total events: 19 (Vitamin E), 11 (Control)					
Heterogeneity: Chi² = 2.94, df = 6 (P = 0.82); I² =0.0%					
Test for overall effect: Z = 1.41 (P = 0.16)					
2 Renal failure or insufficiency					
Gulmezoglu 1997	0/27	1/29		22.5 %	0.36 [0.02, 8.41]
Rumbold 2006	9/935	5/942		77.5 %	1.81 [0.61, 5.39]
Subtotal (95% CI)	**962**	**971**		**100.0 %**	**1.49 [0.55, 4.02]**
Total events: 9 (Vitamin E), 6 (Control)					
Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² =0.0%					
Test for overall effect: Z = 0.78 (P = 0.44)					
3 Disseminated intravascular coagulation					
Gulmezoglu 1997	0/27	1/29		100.0 %	0.36 [0.02, 8.41]
Subtotal (95% CI)	**27**	**29**		**100.0 %**	**0.36 [0.02, 8.41]**
Total events: 0 (Vitamin E), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
4 Pulmonary oedema					
Gulmezoglu 1997	1/27	2/29		12.9 %	0.54 [0.05, 5.59]
McCance 2010	1/375	2/374		13.4 %	0.50 [0.05, 5.48]
Roberts 2010	3/4961	10/4926		67.1 %	0.30 [0.08, 1.08]

```
           0.01   0.1      1     10   100
          Favours vitamin E    Favours control
```

(*Continued* . . .)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rumbold 2006	1/935	1/942		6.7 %	1.01 [0.06, 16.08]
Subtotal (95% CI)	**6298**	**6271**		**100.0 %**	**0.40 [0.16, 1.03]**

Total events: 6 (Vitamin E), 15 (Control)

Heterogeneity: Chi² = 0.72, df = 3 (P = 0.87); I² =0.0%

Test for overall effect: Z = 1.89 (P = 0.058)

```
   0.01   0.1    1    10   100
```
Favours vitamin E   Favours control

Analysis 1.20. Comparison 1 Any vitamin E supplementation, Outcome 20 Gestational age at birth.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 20 Gestational age at birth

Study or subgroup	Control N	Mean(SD)	Vitamin E N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Beazley 2005	52	36.8 (3.6)	48	37.2 (3.9)		3.1 %	-0.40 [-1.87, 1.07]
Borna 2005	30	32.9 (4.1)	30	32.6 (4.1)		1.6 %	0.30 [-1.77, 2.37]
Gungorduk 2014	125	31.9 (2.6)	121	31 (2.6)		11.8 %	0.90 [0.25, 1.55]
Kalpdev 2011	22	37.17 (1.47)	22	36.17 (2.13)		5.4 %	1.00 [-0.08, 2.08]
Nasrolahi 2006	290	38.2 (2.4)	290	38.1 (2.8)		19.2 %	0.10 [-0.32, 0.52]
Poston 2006	1393	37.4 (3.9)	1391	37.6 (3.7)		25.9 %	-0.20 [-0.48, 0.08]
Roberts 2010	4993	38.9 (3.5)	4976	38.8 (3.5)		32.9 %	0.10 [-0.04, 0.24]
Total (95% CI)	**6905**		**6878**			**100.0 %**	**0.15 [-0.12, 0.43]**

Heterogeneity: Tau² = 0.05; Chi² = 13.21, df = 6 (P = 0.04); I² =55%

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

```
   -4    -2    0    2    4
```
Favours vitamin E   Favours control

Analysis 1.21. Comparison 1 Any vitamin E supplementation, Outcome 21 Congenital malformations.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 21 Congenital malformations

Study or subgroup	Vitamin E	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
McCance 2010	12/378	17/382		28.1 %	0.71 [0.35, 1.47]
Spinnato 2007	1/351	2/349		3.3 %	0.50 [0.05, 5.46]
Villar 2009	19/753	12/762		19.8 %	1.60 [0.78, 3.28]
Xu 2010	37/1243	30/1293		48.8 %	1.28 [0.80, 2.06]
Total (95% CI)	**2725**	**2786**		**100.0 %**	**1.16 [0.83, 1.63]**

Total events: 69 (Vitamin E), 61 (Control)

Heterogeneity: Chi² = 3.16, df = 3 (P = 0.37); I² =5%

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable

```
0.1  0.2   0.5   1    2    5   10
Favours vitamin E      Favours control
```

Analysis 1.22. Comparison 1 Any vitamin E supplementation, Outcome 22 Apgar score less than seven at five minutes.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 22 Apgar score less than seven at five minutes

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gulmezoglu 1997	4/20	6/19		22.6 %	0.63 [0.21, 1.90]
Poston 2006	8/1393	9/1391		33.1 %	0.89 [0.34, 2.29]
Spinnato 2007	8/356	12/352		44.3 %	0.66 [0.27, 1.59]
Total (95% CI)	**1769**	**1762**		**100.0 %**	**0.73 [0.42, 1.27]**

Total events: 20 (Vitamin E), 27 (Control)

Heterogeneity: Chi^2 = 0.28, df = 2 (P = 0.87); I^2 =0.0%

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Not applicable

```
        0.2    0.5    1    2    5
     Favours vitamin E   Favours control
```
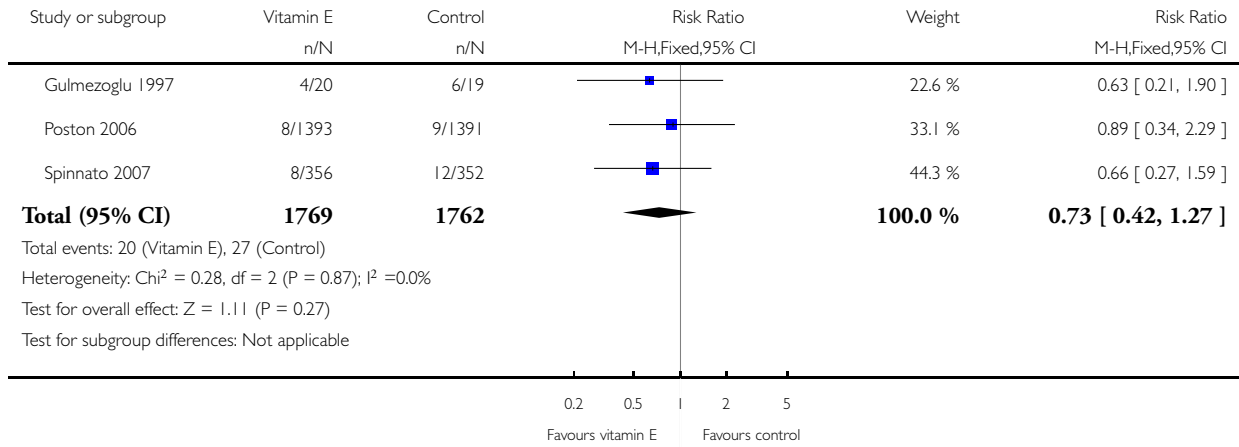
Analysis 1.24.   Comparison 1 Any vitamin E supplementation, Outcome 24 Respiratory distress syndrome.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 24 Respiratory distress syndrome

Study or subgroup	Vitamin E	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Borna 2005	15/30	15/30		2.2 %	1.00 [0.60, 1.66]
Gungorduk 2014	57/124	66/119		10.1 %	0.83 [0.65, 1.06]
McCance 2010	26/363	32/364		4.8 %	0.81 [0.50, 1.34]
Poston 2006	91/1350	89/1364		13.3 %	1.03 [0.78, 1.37]
Roberts 2010	150/4900	144/4881		21.6 %	1.04 [0.83, 1.30]
Rumbold 2006	2/924	12/929		1.8 %	0.17 [0.04, 0.75]
Spinnato 2007	40/344	34/339		5.1 %	1.16 [0.75, 1.79]
Xu 2010	267/1227	281/1286		41.1 %	1.00 [0.86, 1.15]
Total (95% CI)	**9262**	**9312**		**100.0 %**	**0.98 [0.89, 1.08]**

Total events: 648 (Vitamin E), 673 (Control)

Heterogeneity: Chi^2 = 8.63, df = 7 (P = 0.28); I^2 =19%

Test for overall effect: Z = 0.45 (P = 0.66)

Test for subgroup differences: Not applicable

```
        0.1  0.2   0.5   1    2    5   10
       Favours vitamin E      Favours control
```

Analysis 1.25. Comparison 1 Any vitamin E supplementation, Outcome 25 Chronic lung disease or bronchopulmonary dysplasia.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 25 Chronic lung disease or bronchopulmonary dysplasia

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
McCance 2010	2/363	5/363		41.2 %	0.40 [0.08, 2.05]
Rumbold 2006	1/924	5/929		33.9 %	0.20 [0.02, 1.72]
Spinnato 2007	4/344	0/339		24.9 %	8.87 [0.48, 164.11]
Total (95% CI)	**1631**	**1631**		**100.0 %**	**0.69 [0.10, 4.69]**

Total events: 7 (Vitamin E), 10 (Control)

Heterogeneity: Tau^2 = 1.64; Chi^2 = 4.68, df = 2 (P = 0.10); I^2 =57%

Test for overall effect: Z = 0.38 (P = 0.70)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control
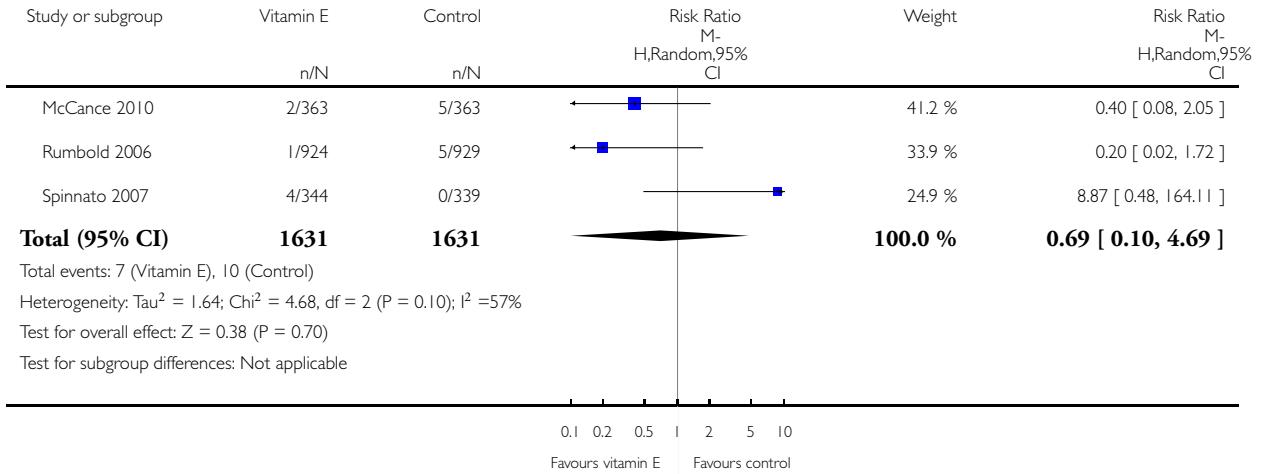
Analysis 1.26. Comparison 1 Any vitamin E supplementation, Outcome 26 Periventricular haemorrhage and periventricular leukomalacia.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 26 Periventricular haemorrhage and periventricular leukomalacia

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gungorduk 2014	6/124	7/119		18.1 %	0.82 [0.28, 2.38]
Poston 2006	10/1350	16/1364		40.4 %	0.63 [0.29, 1.39]
Roberts 2010	6/4900	7/4881		17.8 %	0.85 [0.29, 2.54]
Rumbold 2006	1/924	1/929		2.5 %	1.01 [0.06, 16.05]
Spinnato 2007	1/344	0/339		1.3 %	2.96 [0.12, 72.32]
Xu 2010	11/1227	8/1286		19.8 %	1.44 [0.58, 3.57]
Total (95% CI)	**8869**	**8918**		**100.0 %**	**0.91 [0.58, 1.42]**

Total events: 35 (Vitamin E), 39 (Control)

Heterogeneity: Chi² = 2.39, df = 5 (P = 0.79); I² =0.0%

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control

Analysis 1.27.   Comparison 1 Any vitamin E supplementation, Outcome 27 Bacterial sepsis.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 27 Bacterial sepsis

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Borna 2005	5/30	6/30		11.7 %	0.83 [0.28, 2.44]
Gungorduk 2014	32/124	26/119		32.5 %	1.18 [0.75, 1.86]
McCance 2010	6/363	14/364		14.2 %	0.43 [0.17, 1.11]
Roberts 2010	30/4900	23/4881		27.8 %	1.30 [0.76, 2.23]
Xu 2010	13/1227	6/1286		13.8 %	2.27 [0.87, 5.96]
Total (95% CI)	**6644**	**6680**		**100.0 %**	**1.10 [0.73, 1.67]**

Total events: 86 (Vitamin E), 75 (Control)

Heterogeneity: Tau² = 0.09; Chi² = 6.63, df = 4 (P = 0.16); I² =40%

Test for overall effect: Z = 0.46 (P = 0.64)

Test for subgroup differences: Not applicable

```
      0.1   0.2   0.5    1    2    5   10
     Favours vitamin E      Favours control
```

Analysis 1.28. Comparison 1 Any vitamin E supplementation, Outcome 28 Necrotising enterocolitis.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 28 Necrotising enterocolitis

Study or subgroup	Vitamin E	Control	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Gungorduk 2014	13/124	16/119		29.0 %	0.78 [0.39, 1.55]
McCance 2010	0/362	3/365		5.3 %	0.14 [0.01, 2.78]
Poston 2006	11/1350	4/1364		20.0 %	2.78 [0.89, 8.70]
Roberts 2010	10/4900	14/4881		26.4 %	0.71 [0.32, 1.60]
Rumbold 2006	0/924	2/929		5.1 %	0.20 [0.01, 4.18]
Spinnato 2007	1/344	0/339		4.7 %	2.96 [0.12, 72.32]
Xu 2010	1/1227	9/1286		9.6 %	0.12 [0.01, 0.92]
Total (95% CI)	**9231**	**9283**		**100.0 %**	**0.74 [0.36, 1.55]**

Total events: 36 (Vitamin E), 48 (Control)

Heterogeneity: Tau² = 0.36; Chi² = 10.83, df = 6 (P = 0.09); I² =45%

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control

Analysis 1.29. Comparison 1 Any vitamin E supplementation, Outcome 29 Retinopathy of prematurity.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 29 Retinopathy of prematurity

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McCance 2010	1/361	2/365		6.9 %	0.51 [0.05, 5.55]
Poston 2006	6/1350	6/1364		20.6 %	1.01 [0.33, 3.12]
Roberts 2010	19/4900	16/4881		55.4 %	1.18 [0.61, 2.30]
Rumbold 2006	0/924	1/929		5.2 %	0.34 [0.01, 8.22]
Spinnato 2007	3/344	0/339		1.7 %	6.90 [0.36, 133.05]
Xu 2010	4/1227	3/1286		10.1 %	1.40 [0.31, 6.23]
Total (95% CI)	**9106**	**9164**		**100.0 %**	**1.18 [0.72, 1.93]**

Total events: 33 (Vitamin E), 28 (Control)

Heterogeneity: Chi² = 2.56, df = 5 (P = 0.77); I² =0.0%

Test for overall effect: Z = 0.65 (P = 0.52)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control

Analysis 1.33.   Comparison 1 Any vitamin E supplementation, Outcome 33 Side effects of vitamin E supplementation.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 33 Side effects of vitamin E supplementation

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Acne					
Gulmezoglu 1997	1/27	0/29		100.0 %	3.21 [0.14, 75.68]
Subtotal (95% CI)	**27**	**29**		**100.0 %**	**3.21 [0.14, 75.68]**
Total events: 1 (Vitamin E), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
2 Transient weakness					
Gulmezoglu 1997	2/27	0/29		100.0 %	5.36 [0.27, 106.78]
Subtotal (95% CI)	**27**	**29**		**100.0 %**	**5.36 [0.27, 106.78]**
Total events: 2 (Vitamin E), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
3 Skin rash					
Gulmezoglu 1997	1/27	0/29		100.0 %	3.21 [0.14, 75.68]
Subtotal (95% CI)	**27**	**29**		**100.0 %**	**3.21 [0.14, 75.68]**
Total events: 1 (Vitamin E), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
4 Any side effects (symptoms not reported separately by group status)					
Spinnato 2007	7/355	6/352		100.0 %	1.16 [0.39, 3.41]
Subtotal (95% CI)	**355**	**352**		**100.0 %**	**1.16 [0.39, 3.41]**
Total events: 7 (Vitamin E), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.79)					
5 Abdominal pain					
Rumbold 2006	74/935	45/942		100.0 %	1.66 [1.16, 2.37]
Subtotal (95% CI)	**935**	**942**		**100.0 %**	**1.66 [1.16, 2.37]**
Total events: 74 (Vitamin E), 45 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.75 (P = 0.0059)					
6 Elevated liver enzymes (defined by authors)					
Roberts 2010	35/4993	48/4976		74.0 %	0.73 [0.47, 1.12]
Rumbold 2006	21/935	10/942		15.3 %	2.12 [1.00, 4.47]

0.001 0.01 0.1 1 10 100 1000

Favours vitamin E   Favours control

(*Continued* . . .)

Study or subgroup	Vitamin E	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Xu 2010	9/1167	7/1196		10.6 %	1.32 [0.49, 3.53]
Subtotal (95% CI)	**7095**	**7114**		**100.0 %**	**1.00 [0.71, 1.41]**

Total events: 65 (Vitamin E), 65 (Control)

Heterogeneity: Chi² = 6.24, df = 2 (P = 0.04); I² =68%

Test for overall effect: Z = 0.02 (P = 0.99)

```
        0.001 0.01  0.1   1   10  100 1000
       Favours vitamin E    Favours control
```

Analysis 1.34. Comparison 1 Any vitamin E supplementation, Outcome 34 Use of health service resources - maternal.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 34 Use of health service resources - maternal

Study or subgroup	Vitamin E	Control	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
1 Admission to intensive care unit					
Villar 2009	1/681	5/674		27.2 %	0.20 [0.02, 1.69]
Xu 2010	16/1167	18/1196		72.8 %	0.91 [0.47, 1.78]
Subtotal (95% CI)	**1848**	**1870**		**100.0 %**	**0.60 [0.16, 2.30]**
Total events: 17 (Vitamin E), 23 (Control)					
Heterogeneity: Tau² = 0.53; Chi² = 1.80, df = 1 (P = 0.18); I² =45%					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 Hospitalisations in pregnancy					
Kalpdev 2011	3/22	8/22		31.2 %	0.38 [0.11, 1.23]
Xu 2010	333/1167	341/1196		68.8 %	1.00 [0.88, 1.14]
Subtotal (95% CI)	**1189**	**1218**		**100.0 %**	**0.74 [0.30, 1.80]**
Total events: 336 (Vitamin E), 349 (Control)					
Heterogeneity: Tau² = 0.30; Chi² = 2.60, df = 1 (P = 0.11); I² =61%					
Test for overall effect: Z = 0.67 (P = 0.50)					
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² =0.0%					

```
        0.1  0.2   0.5   1   2   5   10
       Favours vitamin E    Favours control
```

Analysis 1.35. Comparison 1 Any vitamin E supplementation, Outcome 35 Use of health service resources - infant.

Review: Vitamin E supplementation in pregnancy

Comparison: 1 Any vitamin E supplementation

Outcome: 35 Use of health service resources - infant

Study or subgroup	Vitamin E	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Admission to intensive care unit					
Borna 2005	23/30	22/30		1.8 %	1.05 [0.78, 1.40]
Gulmezoglu 1997	5/20	6/20		0.5 %	0.83 [0.30, 2.29]
Gungorduk 2014	77/124	83/119		6.7 %	0.89 [0.74, 1.07]
McCance 2010	197/363	205/365		16.3 %	0.97 [0.85, 1.10]
Poston 2006	280/1350	255/1364		20.2 %	1.11 [0.95, 1.29]
Roberts 2010	577/4900	557/4881		44.5 %	1.03 [0.92, 1.15]
Villar 2009	64/753	80/762		6.3 %	0.81 [0.59, 1.11]
Xu 2010	46/1227	48/1286		3.7 %	1.00 [0.68, 1.49]
Subtotal (95% CI)	**8767**	**8827**		**100.0 %**	**1.01 [0.95, 1.08]**
Total events: 1269 (Vitamin E), 1256 (Control)					
Heterogeneity: Chi² = 6.05, df = 7 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 Use of mechanical ventilation					
Gulmezoglu 1997	2/20	6/20		3.4 %	0.33 [0.08, 1.46]
McCance 2010	20/364	25/364		14.1 %	0.80 [0.45, 1.41]
Poston 2006	74/1350	58/1364		32.5 %	1.29 [0.92, 1.80]
Rumbold 2006	13/924	23/929		12.9 %	0.57 [0.29, 1.11]
Spinnato 2007	16/344	13/339		7.4 %	1.21 [0.59, 2.48]
Xu 2010	55/1227	54/1286		29.7 %	1.07 [0.74, 1.54]
Subtotal (95% CI)	**4229**	**4302**		**100.0 %**	**1.02 [0.84, 1.25]**
Total events: 180 (Vitamin E), 179 (Control)					
Heterogeneity: Chi² = 7.95, df = 5 (P = 0.16); I² =37%					
Test for overall effect: Z = 0.22 (P = 0.82)					

0.01   0.1   1   10   100

Favours vitamin E   Favours control

Analysis 2.1. Comparison 2 Any vitamin E supplementation (sensitivity analyses by trial quality), Outcome 1 Stillbirth.

Review: Vitamin E supplementation in pregnancy

Comparison: 2 Any vitamin E supplementation (sensitivity analyses by trial quality)

Outcome: 1 Stillbirth

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low overall risk of bias					
Chappell 1999	1/141	2/142		2.4 %	0.50 [0.05, 5.49]
Gulmezoglu 1997	7/27	9/29		10.4 %	0.84 [0.36, 1.93]
McCance 2010	9/373	8/373		9.6 %	1.13 [0.44, 2.88]
Poston 2006	19/1369	7/1372		8.4 %	2.72 [1.15, 6.45]
Roberts 2010	38/4938	36/4917		43.1 %	1.05 [0.67, 1.66]
Rumbold 2006	8/932	6/935		7.2 %	1.34 [0.47, 3.84]
Spinnato 2007	7/351	10/349		12.0 %	0.70 [0.27, 1.81]
Xu 2010	10/1237	6/1292		7.0 %	1.74 [0.63, 4.78]
Total (95% CI)	**9368**	**9409**		**100.0 %**	**1.19 [0.89, 1.58]**

Total events: 99 (Vitamin E), 84 (Control)

Heterogeneity: Chi^2 = 6.81, df = 7 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 1.19 (P = 0.24)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours vitamin E   Favours control

Analysis 2.2. Comparison 2 Any vitamin E supplementation (sensitivity analyses by trial quality), Outcome 2 Neonatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 2 Any vitamin E supplementation (sensitivity analyses by trial quality)

Outcome: 2 Neonatal death

Study or subgroup	Vitamin E	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Low overall risk of bias					
Gulmezoglu 1997	5/20	1/20		1.8 %	5.00 [0.64, 39.06]
McCance 2010	2/364	3/366		5.3 %	0.67 [0.11, 3.99]
Poston 2006	8/1350	12/1364		21.3 %	0.67 [0.28, 1.64]
Roberts 2010	20/4900	27/4881		48.4 %	0.74 [0.41, 1.31]
Rumbold 2006	1/924	4/929		7.1 %	0.25 [0.03, 2.24]
Spinnato 2007	6/344	6/339		10.8 %	0.99 [0.32, 3.03]
Xu 2010	5/1227	3/1286		5.2 %	1.75 [0.42, 7.29]
Total (95% CI)	**9129**	**9185**		**100.0 %**	**0.84 [0.57, 1.24]**

Total events: 47 (Vitamin E), 56 (Control)

Heterogeneity: Chi² = 5.64, df = 6 (P = 0.46); I² =0.0%

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable

```
        0.01   0.1    I    I0   100
        Favours vitamin E   Favours control
```

Analysis 2.3. Comparison 2 Any vitamin E supplementation (sensitivity analyses by trial quality), Outcome 3 Perinatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 2 Any vitamin E supplementation (sensitivity analyses by trial quality)

Outcome: 3 Perinatal death

Study or subgroup	Favours vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low overall risk of bias					
Gulmezoglu 1997	12/27	10/29		19.7 %	1.29 [0.67, 2.48]
Poston 2006	43/1383	27/1391		27.5 %	1.60 [1.00, 2.58]
Roberts 2010	12/4993	11/4976		14.8 %	1.09 [0.48, 2.46]
Villar 2009	56/753	68/762		35.2 %	0.83 [0.59, 1.17]
Xu 2010	5/1167	1/1196		2.9 %	5.12 [0.60, 43.79]
Total (95% CI)	**8323**	**8354**		**100.0 %**	**1.19 [0.82, 1.73]**

Total events: 128 (Favours vitamin E), 117 (Control)

Heterogeneity: Tau² = 0.07; Chi² = 7.19, df = 4 (P = 0.13); I² =44%

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Not applicable

```
         0.1  0.2  0.5   I    2    5   10
         Favours vitamin E    Favours control
```
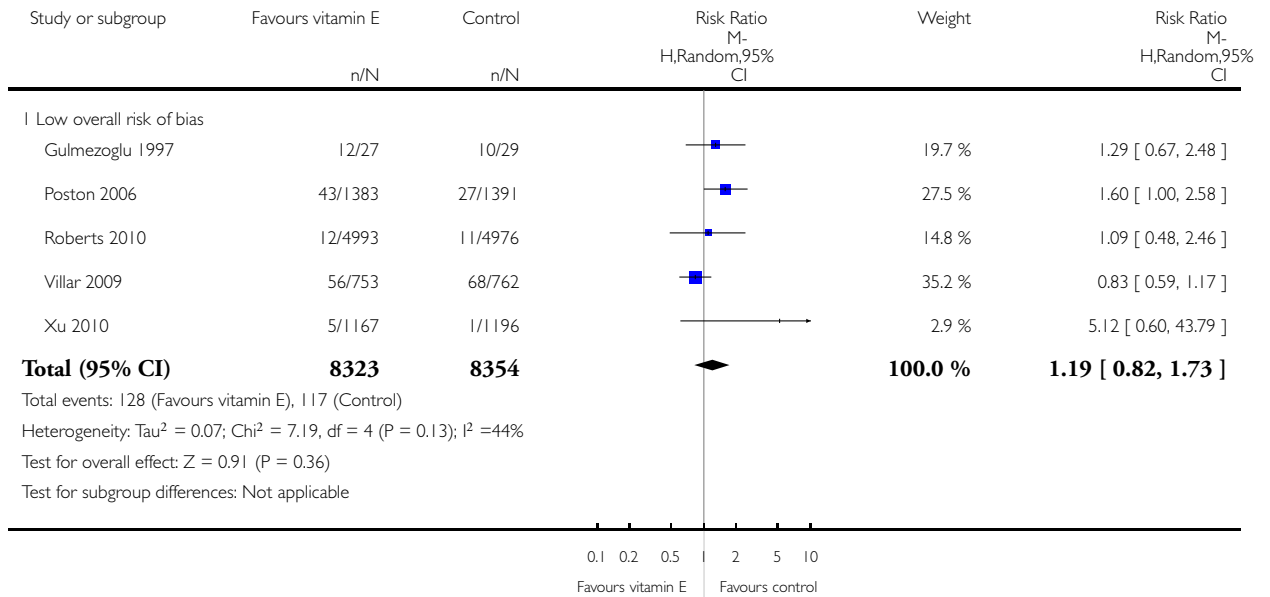
Analysis 2.4.   Comparison 2 Any vitamin E supplementation (sensitivity analyses by trial quality), Outcome 4 Preterm birth (< 37 weeks' gestation).

Review: Vitamin E supplementation in pregnancy

Comparison: 2 Any vitamin E supplementation (sensitivity analyses by trial quality)

Outcome: 4 Preterm birth (< 37 weeks' gestation)

Study or subgroup	Vitamin E	Control	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
1 Low overall risk of bias					
Chappell 1999	6/141	5/142		0.5 %	1.21 [0.38, 3.87]
McCance 2010	126/375	152/374		13.0 %	0.83 [0.69, 1.00]
Poston 2006	400/1372	373/1376		21.9 %	1.08 [0.95, 1.21]
Roberts 2010	513/4993	526/4976		22.7 %	0.97 [0.87, 1.09]
Rumbold 2006	64/935	63/942		5.1 %	1.02 [0.73, 1.43]
Spinnato 2007	96/351	82/349		8.2 %	1.16 [0.90, 1.50]
Villar 2009	188/674	213/669		15.4 %	0.88 [0.74, 1.03]
Xu 2010	193/1243	184/1293		13.1 %	1.09 [0.91, 1.31]
Total (95% CI)	**10084**	**10121**		**100.0 %**	**0.99 [0.91, 1.07]**

Total events: 1586 (Vitamin E), 1598 (Control)

Heterogeneity: Tau^2 = 0.00; Chi^2 = 10.36, df = 7 (P = 0.17); I^2 =32%

Test for overall effect: Z = 0.23 (P = 0.82)

Test for subgroup differences: Not applicable

0.1   0.2   0.5   1   2   5   10

Favours vitamin E   Favours control

Analysis 2.5. Comparison 2 Any vitamin E supplementation (sensitivity analyses by trial quality), Outcome 5 Clinical pre-eclampsia.

Review: Vitamin E supplementation in pregnancy

Comparison: 2 Any vitamin E supplementation (sensitivity analyses by trial quality)

Outcome: 5 Clinical pre-eclampsia

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 Low overall risk of bias					
Chappell 1999	11/141	24/142		2.3 %	0.46 [0.24, 0.91]
McCance 2010	57/375	70/374		9.0 %	0.81 [0.59, 1.12]
Poston 2006	181/1196	187/1199		19.7 %	0.97 [0.80, 1.17]
Roberts 2010	358/4993	332/4976		26.7 %	1.07 [0.93, 1.24]
Rumbold 2006	56/935	47/942		6.8 %	1.20 [0.82, 1.75]
Spinnato 2007	49/355	55/352		7.5 %	0.88 [0.62, 1.26]
Villar 2009	164/681	157/674		19.3 %	1.03 [0.85, 1.25]
Xu 2010	69/1167	68/1196		8.7 %	1.04 [0.75, 1.44]
Total (95% CI)	**9843**	**9855**		**100.0 %**	**0.99 [0.89, 1.10]**

Total events: 945 (Vitamin E), 940 (Control)

Heterogeneity: Tau^2 = 0.01; Chi^2 = 9.27, df = 7 (P = 0.23); I^2 =25%

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable

```
        0.1  0.2   0.5   1    2    5   10
        Favours vitamin E      Favours control
```

Analysis 2.6.   Comparison 2 Any vitamin E supplementation (sensitivity analyses by trial quality), Outcome 6 Intrauterine growth restriction.

Review: Vitamin E supplementation in pregnancy

Comparison: 2 Any vitamin E supplementation (sensitivity analyses by trial quality)

Outcome: 6 Intrauterine growth restriction

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low overall risk of bias					
Chappell 1999	33/141	45/142		4.2 %	0.74 [0.50, 1.08]
McCance 2010	23/373	36/372		3.4 %	0.64 [0.39, 1.05]
Poston 2006	403/1385	360/1386		34.1 %	1.12 [0.99, 1.26]
Roberts 2010	133/4900	132/4881		12.5 %	1.00 [0.79, 1.27]
Rumbold 2006	80/924	92/929		8.7 %	0.87 [0.66, 1.16]
Spinnato 2007	49/356	49/352		4.7 %	0.99 [0.68, 1.43]
Villar 2009	141/592	149/573		14.3 %	0.92 [0.75, 1.12]
Xu 2010	173/1243	194/1293		18.0 %	0.93 [0.77, 1.12]
Total (95% CI)	**9914**	**9928**		**100.0 %**	**0.98 [0.91, 1.06]**

Total events: 1035 (Vitamin E), 1057 (Control)

Heterogeneity: Chi^2 = 10.99, df = 7 (P = 0.14); I^2 =36%

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable

0.1   0.2   0.5   1   2   5   10

Favours vitamin E   Favours control

Analysis 3.1. Comparison 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry), Outcome 1 Stillbirth.

Review: Vitamin E supplementation in pregnancy

Comparison: 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry)

Outcome: 1 Stillbirth

Study or subgroup	Vitamin E	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Less than or equal to 20 week's gestation					
Roberts 2010	38/4938	36/4917		42.1 %	1.05 [0.67, 1.66]
Spinnato 2007	7/351	10/349		11.7 %	0.70 [0.27, 1.81]
Xu 2010	10/1237	6/1292		6.9 %	1.74 [0.63, 4.78]
Subtotal (95% CI)	**6526**	**6558**		**60.7 %**	**1.06 [0.73, 1.55]**
Total events: 55 (Vitamin E), 52 (Control)					
Heterogeneity: Chi² = 1.68, df = 2 (P = 0.43); I² =0.0%					
Test for overall effect: Z = 0.31 (P = 0.76)					
2 Greater than 20 weeks' gestation					
Gulmezoglu 1997	7/27	9/29		10.1 %	0.84 [0.36, 1.93]
Gungorduk 2014	1/125	2/121		2.4 %	0.48 [0.04, 5.27]
Subtotal (95% CI)	**152**	**150**		**12.5 %**	**0.77 [0.35, 1.70]**
Total events: 8 (Vitamin E), 11 (Control)					
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² =0.0%					
Test for overall effect: Z = 0.65 (P = 0.52)					
3 Both prior to and after 20 weeks' gestation					
Chappell 1999	1/141	2/142		2.3 %	0.50 [0.05, 5.49]
McCance 2010	9/373	8/373		9.3 %	1.13 [0.44, 2.88]
Poston 2006	19/1369	7/1372		8.2 %	2.72 [1.15, 6.45]
Rumbold 2006	8/932	6/935		7.0 %	1.34 [0.47, 3.84]
Subtotal (95% CI)	**2815**	**2822**		**26.8 %**	**1.61 [0.96, 2.70]**
Total events: 37 (Vitamin E), 23 (Control)					
Heterogeneity: Chi² = 3.00, df = 3 (P = 0.39); I² =0%					
Test for overall effect: Z = 1.81 (P = 0.070)					
Total (95% CI)	**9493**	**9530**		**100.0 %**	**1.17 [0.88, 1.56]**
Total events: 100 (Vitamin E), 86 (Control)					
Heterogeneity: Chi² = 7.31, df = 8 (P = 0.50); I² =0.0%					
Test for overall effect: Z = 1.10 (P = 0.27)					
Test for subgroup differences: Chi² = 2.80, df = 2 (P = 0.25), I² =29%					

0.01   0.1   1   10   100

Favours vitamin E   Favours control

Analysis 3.2. Comparison 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry), Outcome 2 Neonatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry)

Outcome: 2 Neonatal death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Less than or equal to 20 weeks' gestation					
Roberts 2010	20/4900	27/4881		36.0 %	0.74 [0.41, 1.31]
Spinnato 2007	6/344	6/339		8.0 %	0.99 [0.32, 3.03]
Xu 2010	5/1227	3/1286		3.9 %	1.75 [0.42, 7.29]
Subtotal (95% CI)	**6471**	**6506**		**47.9 %**	**0.86 [0.53, 1.39]**
Total events: 31 (Vitamin E), 36 (Control)					
Heterogeneity: Chi² = 1.27, df = 2 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 0.61 (P = 0.54)					
2 Greater than 20 weeks' gestation					
Borna 2005	4/30	5/30		6.6 %	0.80 [0.24, 2.69]
Gulmezoglu 1997	5/20	1/20		1.3 %	5.00 [0.64, 39.06]
Gungorduk 2014	10/124	14/119		19.0 %	0.69 [0.32, 1.48]
Subtotal (95% CI)	**174**	**169**		**27.0 %**	**0.93 [0.51, 1.68]**
Total events: 19 (Vitamin E), 20 (Control)					
Heterogeneity: Chi² = 3.23, df = 2 (P = 0.20); I² =38%					
Test for overall effect: Z = 0.25 (P = 0.80)					
3 Both prior to and after 20 weeks' gestation					
McCance 2010	2/364	3/366		4.0 %	0.67 [0.11, 3.99]
Poston 2006	8/1350	12/1364		15.9 %	0.67 [0.28, 1.64]
Rumbold 2006	1/924	4/929		5.3 %	0.25 [0.03, 2.24]
Subtotal (95% CI)	**2638**	**2659**		**25.1 %**	**0.58 [0.28, 1.22]**
Total events: 11 (Vitamin E), 19 (Control)					
Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² =0.0%					
Test for overall effect: Z = 1.42 (P = 0.15)					
Total (95% CI)	**9283**	**9334**		**100.0 %**	**0.81 [0.58, 1.13]**
Total events: 61 (Vitamin E), 75 (Control)					
Heterogeneity: Chi² = 5.82, df = 8 (P = 0.67); I² =0.0%					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Chi² = 1.01, df = 2 (P = 0.60), I² =0.0%					

```
         0.01   0.1    1    10   100
      Favours vitamin E    Favours control
```

Analysis 3.3.   Comparison 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry), Outcome 3 Perinatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry)

Outcome: 3 Perinatal death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 Less than or equal to 20 weeks' gestation					
Roberts 2010	12/4993	11/4976		12.6 %	1.09 [0.48, 2.46]
Xu 2010	5/1167	1/1196		2.4 %	5.12 [0.60, 43.79]
Subtotal (95% CI)	**6160**	**6172**		**15.0 %**	**1.71 [0.42, 6.87]**
Total events: 17 (Vitamin E), 12 (Control)					
Heterogeneity: Tau² = 0.54; Chi² = 1.78, df = 1 (P = 0.18); I² =44%					
Test for overall effect: Z = 0.75 (P = 0.45)					
2 Greater than 20 weeks' gestation					
Gulmezoglu 1997	12/27	10/29		16.8 %	1.29 [0.67, 2.48]
Gungorduk 2014	11/125	16/121		14.8 %	0.67 [0.32, 1.38]
Subtotal (95% CI)	**152**	**150**		**31.5 %**	**0.94 [0.49, 1.82]**
Total events: 23 (Vitamin E), 26 (Control)					
Heterogeneity: Tau² = 0.10; Chi² = 1.82, df = 1 (P = 0.18); I² =45%					
Test for overall effect: Z = 0.17 (P = 0.86)					
3 Both prior to and after 20 weeks' gestation					
Poston 2006	43/1383	27/1391		23.5 %	1.60 [1.00, 2.58]
Villar 2009	56/753	68/762		30.0 %	0.83 [0.59, 1.17]
Subtotal (95% CI)	**2136**	**2153**		**53.5 %**	**1.13 [0.60, 2.14]**
Total events: 99 (Vitamin E), 95 (Control)					
Heterogeneity: Tau² = 0.17; Chi² = 4.82, df = 1 (P = 0.03); I² =79%					
Test for overall effect: Z = 0.37 (P = 0.71)					
Total (95% CI)	**8448**	**8475**		**100.0 %**	**1.09 [0.77, 1.54]**
Total events: 139 (Vitamin E), 133 (Control)					
Heterogeneity: Tau² = 0.07; Chi² = 8.82, df = 5 (P = 0.12); I² =43%					
Test for overall effect: Z = 0.50 (P = 0.61)					
Test for subgroup differences: Chi² = 0.59, df = 2 (P = 0.74), I² =0.0%					

```
        0.1   0.2   0.5    1    2    5    10

        Favours vitamin E         Favours control
```

Analysis 3.4. Comparison 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry), Outcome 4 Preterm birth.

Review: Vitamin E supplementation in pregnancy

Comparison: 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry)

Outcome: 4 Preterm birth

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Less than or equal to 20 weeks' gestation					
Huria 2010	5/107	16/109		1.1 %	0.32 [0.12, 0.84]
Kalpdev 2011	3/22	10/22		0.8 %	0.30 [0.10, 0.94]
Roberts 2010	513/4993	526/4976		18.0 %	0.97 [0.87, 1.09]
Spinnato 2007	96/351	82/349		9.9 %	1.16 [0.90, 1.50]
Xu 2010	193/1243	184/1293		13.4 %	1.09 [0.91, 1.31]
Subtotal (95% CI)	**6716**	**6749**		**43.3 %**	**0.96 [0.77, 1.20]**
Total events: 810 (Vitamin E), 818 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 12.06, df = 4 (P = 0.02); I^2 =67%					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 Greater than 20 weeks' gestation					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vitamin E), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Both prior to and after 20 weeks' gestation					
Beazley 2005	20/52	14/48		3.1 %	1.32 [0.75, 2.31]
Chappell 1999	6/141	5/142		0.8 %	1.21 [0.38, 3.87]
McCance 2010	126/375	152/374		13.3 %	0.83 [0.69, 1.00]
Poston 2006	400/1372	373/1376		17.7 %	1.08 [0.95, 1.21]
Rumbold 2006	64/935	63/942		7.0 %	1.02 [0.73, 1.43]
Villar 2009	188/674	213/669		14.8 %	0.88 [0.74, 1.03]
Subtotal (95% CI)	**3549**	**3551**		**56.7 %**	**0.96 [0.85, 1.10]**
Total events: 804 (Vitamin E), 820 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 8.52, df = 5 (P = 0.13); I^2 =41%					
Test for overall effect: Z = 0.57 (P = 0.57)					
Total (95% CI)	**10265**	**10300**		**100.0 %**	**0.98 [0.88, 1.09]**
Total events: 1614 (Vitamin E), 1638 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 20.80, df = 10 (P = 0.02); I^2 =52%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 1.00), I^2 =0.0%					

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control

Analysis 3.5. Comparison 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry), Outcome 5 Clinical pre-eclampsia.

Review: Vitamin E supplementation in pregnancy

Comparison: 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry)

Outcome: 5 Clinical pre-eclampsia

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Less than or equal to 20 weeks' gestation					
Huria 2010	5/107	11/109		1.9 %	0.46 [0.17, 1.29]
Kalpdev 2011	2/22	3/22		0.7 %	0.67 [0.12, 3.61]
Roberts 2010	358/4993	332/4976		17.5 %	1.07 [0.93, 1.24]
Spinnato 2007	49/355	55/352		9.4 %	0.88 [0.62, 1.26]
Xu 2010	69/1167	68/1196		10.4 %	1.04 [0.75, 1.44]
Subtotal (95% CI)	**6644**	**6655**		**39.9 %**	**1.03 [0.91, 1.16]**
Total events: 483 (Vitamin E), 469 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 3.65, df = 4 (P = 0.45); I² =0.0%					
Test for overall effect: Z = 0.47 (P = 0.64)					
2 Greater than 20 weeks' gestation					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vitamin E), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Both prior to and after 20 weeks' gestation					
Beazley 2005	9/52	9/48		2.7 %	0.92 [0.40, 2.13]
Chappell 1999	11/141	24/142		3.9 %	0.46 [0.24, 0.91]
McCance 2010	57/375	70/374		10.6 %	0.81 [0.59, 1.12]
Poston 2006	181/1196	187/1199		15.6 %	0.97 [0.80, 1.17]
Rivas 2000	1/63	14/64		0.5 %	0.07 [0.01, 0.54]
Rumbold 2006	56/935	47/942		8.8 %	1.20 [0.82, 1.75]
Villar 2009	164/681	157/674		15.5 %	1.03 [0.85, 1.25]
Subtotal (95% CI)	**3443**	**3443**		**57.7 %**	**0.90 [0.73, 1.12]**
Total events: 479 (Vitamin E), 508 (Control)					

0.001 0.01 0.1 1 10 100 1000

Favours vitamin E　　Favours control

(*Continued* . . .)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Heterogeneity: Tau² = 0.04; Chi² = 14.06, df = 6 (P = 0.03); I² =57%					
Test for overall effect: Z = 0.93 (P = 0.35)					
4 Gestation at trial entry unknown					
Mahdy 2004	1/46	2/67		0.4 %	0.73 [0.07, 7.80]
Nasrolahi 2006	5/290	18/290		2.0 %	0.28 [0.10, 0.74]
Subtotal (95% CI)	**336**	**357**		**2.4 %**	**0.32 [0.13, 0.79]**
Total events: 6 (Vitamin E), 20 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.54, df = 1 (P = 0.46); I² =0.0%					
Test for overall effect: Z = 2.47 (P = 0.013)					
Total (95% CI)	**10423**	**10455**		**100.0 %**	**0.91 [0.79, 1.06]**
Total events: 968 (Vitamin E), 997 (Control)					
Heterogeneity: Tau² = 0.03; Chi² = 24.90, df = 13 (P = 0.02); I² =48%					
Test for overall effect: Z = 1.22 (P = 0.22)					
Test for subgroup differences: Chi² = 7.11, df = 2 (P = 0.03), I² =72%					

0.001 0.01 0.1   1   10 100 1000

Favours vitamin E   Favours control

Analysis 3.6. Comparison 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry), Outcome 6 Intrauterine growth restriction.

Review: Vitamin E supplementation in pregnancy

Comparison: 3 Any vitamin E supplementation (subgroup analyses based on gestation at entry)

Outcome: 6 Intrauterine growth restriction

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Less than or equal to 20 week's gestation					
Huria 2010	12/107	13/109		1.2 %	0.94 [0.45, 1.97]
Kalpdev 2011	3/22	2/22		0.2 %	1.50 [0.28, 8.12]
Roberts 2010	133/4900	132/4881		12.3 %	1.00 [0.79, 1.27]
Spinnato 2007	49/356	49/352		4.6 %	0.99 [0.68, 1.43]
Xu 2010	173/1243	194/1293		17.7 %	0.93 [0.77, 1.12]
Subtotal (95% CI)	**6628**	**6657**		**36.0 %**	**0.96 [0.84, 1.10]**
Total events: 370 (Vitamin E), 390 (Control)					
Heterogeneity: Chi² = 0.56, df = 4 (P = 0.97); I² =0.0%					
Test for overall effect: Z = 0.52 (P = 0.60)					
2 Greater than 20 weeks' gestation					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vitamin E), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Both prior to and after 20 weeks' gestation					
Beazley 2005	2/52	4/48		0.4 %	0.46 [0.09, 2.41]
Chappell 1999	33/141	45/142		4.2 %	0.74 [0.50, 1.08]
McCance 2010	23/373	36/372		3.4 %	0.64 [0.39, 1.05]
Poston 2006	403/1385	360/1386		33.5 %	1.12 [0.99, 1.26]
Rumbold 2006	80/924	92/929		8.5 %	0.87 [0.66, 1.16]
Villar 2009	141/592	149/573		14.1 %	0.92 [0.75, 1.12]
Subtotal (95% CI)	**3467**	**3450**		**64.0 %**	**0.99 [0.90, 1.08]**
Total events: 682 (Vitamin E), 686 (Control)					
Heterogeneity: Chi² = 11.33, df = 5 (P = 0.05); I² =56%					
Test for overall effect: Z = 0.25 (P = 0.80)					
Total (95% CI)	**10095**	**10107**		**100.0 %**	**0.98 [0.91, 1.06]**
Total events: 1052 (Vitamin E), 1076 (Control)					
Heterogeneity: Chi² = 12.06, df = 10 (P = 0.28); I² =17%					
Test for overall effect: Z = 0.52 (P = 0.60)					
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² =0.0%					

0.01 0.1 1 10 100

Favours vitamin E   Favours control

Analysis 4.1. Comparison 4 Any vitamin E supplementation (subgroup analyses by dietary intake), Outcome 1 Stillbirth.

Review: Vitamin E supplementation in pregnancy

Comparison: 4 Any vitamin E supplementation (subgroup analyses by dietary intake)

Outcome: 1 Stillbirth

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low dietary intake					
Rumbold 2006	8/932	6/935		7.0 %	1.34 [0.47, 3.84]
Subtotal (95% CI)	**932**	**935**		**7.0 %**	**1.34 [0.47, 3.84]**
Total events: 8 (Vitamin E), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
2 Adequate dietary intake					
Roberts 2010	38/4938	36/4917		42.1 %	1.05 [0.67, 1.66]
Subtotal (95% CI)	**4938**	**4917**		**42.1 %**	**1.05 [0.67, 1.66]**
Total events: 38 (Vitamin E), 36 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					
3 Dietary intake unclear					
Chappell 1999	1/141	2/142		2.3 %	0.50 [0.05, 5.49]
Gulmezoglu 1997	7/27	9/29		10.1 %	0.84 [0.36, 1.93]
Gungorduk 2014	1/125	2/121		2.4 %	0.48 [0.04, 5.27]
McCance 2010	9/373	8/373		9.3 %	1.13 [0.44, 2.88]
Poston 2006	19/1369	7/1372		8.2 %	2.72 [1.15, 6.45]
Spinnato 2007	7/351	10/349		11.7 %	0.70 [0.27, 1.81]
Xu 2010	10/1237	6/1292		6.9 %	1.74 [0.63, 4.78]
Subtotal (95% CI)	**3623**	**3678**		**50.9 %**	**1.25 [0.85, 1.84]**
Total events: 54 (Vitamin E), 44 (Control)					
Heterogeneity: Chi² = 7.08, df = 6 (P = 0.31); I² =15%					
Test for overall effect: Z = 1.13 (P = 0.26)					
Total (95% CI)	**9493**	**9530**		**100.0 %**	**1.17 [0.88, 1.56]**
Total events: 100 (Vitamin E), 86 (Control)					
Heterogeneity: Chi² = 7.31, df = 8 (P = 0.50); I² =0.0%					
Test for overall effect: Z = 1.10 (P = 0.27)					
Test for subgroup differences: Chi² = 0.39, df = 2 (P = 0.82), I² =0.0%					

0.01 0.1 1 10 100

Favours vitamin E   Favours control

Analysis 4.2. Comparison 4 Any vitamin E supplementation (subgroup analyses by dietary intake), Outcome 2 Neonatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 4 Any vitamin E supplementation (subgroup analyses by dietary intake)

Outcome: 2 Neonatal death

Study or subgroup	Vitamin E	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Low dietary intake					
Rumbold 2006	1/924	4/929		5.3 %	0.25 [0.03, 2.24]
Subtotal (95% CI)	**924**	**929**		**5.3 %**	**0.25 [0.03, 2.24]**
Total events: 1 (Vitamin E), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.22)					
2 Adequate dietary intake					
Roberts 2010	20/4900	27/4881		36.0 %	0.74 [0.41, 1.31]
Subtotal (95% CI)	**4900**	**4881**		**36.0 %**	**0.74 [0.41, 1.31]**
Total events: 20 (Vitamin E), 27 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
3 Dietary intake unclear					
Borna 2005	4/30	5/30		6.6 %	0.80 [0.24, 2.69]
Gulmezoglu 1997	5/20	1/20		1.3 %	5.00 [0.64, 39.06]
Gungorduk 2014	10/124	14/119		19.0 %	0.69 [0.32, 1.48]
McCance 2010	2/364	3/366		4.0 %	0.67 [0.11, 3.99]
Poston 2006	8/1350	12/1364		15.9 %	0.67 [0.28, 1.64]
Spinnato 2007	6/344	6/339		8.0 %	0.99 [0.32, 3.03]
Xu 2010	5/1227	3/1286		3.9 %	1.75 [0.42, 7.29]
Subtotal (95% CI)	**3459**	**3524**		**58.7 %**	**0.90 [0.60, 1.37]**
Total events: 40 (Vitamin E), 44 (Control)					
Heterogeneity: Chi² = 4.56, df = 6 (P = 0.60); I² =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
Total (95% CI)	**9283**	**9334**		**100.0 %**	**0.81 [0.58, 1.13]**
Total events: 61 (Vitamin E), 75 (Control)					
Heterogeneity: Chi² = 5.82, df = 8 (P = 0.67); I² =0.0%					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Chi² = 1.46, df = 2 (P = 0.48), I² =0.0%					

0.01   0.1   1   10   100

Favours vitamin E   Favours control

Analysis 4.3. Comparison 4 Any vitamin E supplementation (subgroup analyses by dietary intake), Outcome 3 Perinatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 4 Any vitamin E supplementation (subgroup analyses by dietary intake)

Outcome: 3 Perinatal death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 "Low nutritional status"					
Villar 2009	56/753	68/762		30.0 %	0.83 [0.59, 1.17]
Subtotal (95% CI)	**753**	**762**		**30.0 %**	**0.83 [0.59, 1.17]**
Total events: 56 (Vitamin E), 68 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
2 Adequate dietary intake					
Roberts 2010	12/4993	11/4976		12.6 %	1.09 [0.48, 2.46]
Subtotal (95% CI)	**4993**	**4976**		**12.6 %**	**1.09 [0.48, 2.46]**
Total events: 12 (Vitamin E), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
3 Dietary intake unclear					
Gulmezoglu 1997	12/27	10/29		16.8 %	1.29 [0.67, 2.48]
Gungorduk 2014	11/125	16/121		14.8 %	0.67 [0.32, 1.38]
Poston 2006	43/1383	27/1391		23.5 %	1.60 [1.00, 2.58]
Xu 2010	5/1167	1/1196		2.4 %	5.12 [0.60, 43.79]
Subtotal (95% CI)	**2702**	**2737**		**57.4 %**	**1.26 [0.75, 2.11]**
Total events: 71 (Vitamin E), 54 (Control)					
Heterogeneity: Tau^2 = 0.12; Chi^2 = 5.61, df = 3 (P = 0.13); I^2 =46%					
Test for overall effect: Z = 0.89 (P = 0.38)					
Total (95% CI)	**8448**	**8475**		**100.0 %**	**1.09 [0.77, 1.54]**
Total events: 139 (Vitamin E), 133 (Control)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 8.82, df = 5 (P = 0.12); I^2 =43%					
Test for overall effect: Z = 0.50 (P = 0.61)					
Test for subgroup differences: Chi^2 = 1.84, df = 2 (P = 0.40), I^2 =0.0%					

0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control

Analysis 4.4. Comparison 4 Any vitamin E supplementation (subgroup analyses by dietary intake), Outcome 4 Preterm birth (less than 37 weeks' gestation).

Review: Vitamin E supplementation in pregnancy

Comparison: 4 Any vitamin E supplementation (subgroup analyses by dietary intake)

Outcome: 4 Preterm birth (less than 37 weeks' gestation)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 "Low nutritional status"					
Villar 2009	188/674	213/669		14.8 %	0.88 [0.74, 1.03]
Subtotal (95% CI)	**674**	**669**		**14.8 %**	**0.88 [0.74, 1.03]**
Total events: 188 (Vitamin E), 213 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.58 (P = 0.11)					
2 Low dietary intake					
Rumbold 2006	64/935	63/942		7.0 %	1.02 [0.73, 1.43]
Subtotal (95% CI)	**935**	**942**		**7.0 %**	**1.02 [0.73, 1.43]**
Total events: 64 (Vitamin E), 63 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
3 Adequate dietary intake					
Roberts 2010	513/4993	526/4976		18.0 %	0.97 [0.87, 1.09]
Subtotal (95% CI)	**4993**	**4976**		**18.0 %**	**0.97 [0.87, 1.09]**
Total events: 513 (Vitamin E), 526 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
4 Dietary intake unclear					
Beazley 2005	20/52	14/48		3.1 %	1.32 [0.75, 2.31]
Chappell 1999	6/141	5/142		0.8 %	1.21 [0.38, 3.87]
Huria 2010	5/107	16/109		1.1 %	0.32 [0.12, 0.84]
Kalpdev 2011	3/22	10/22		0.8 %	0.30 [0.10, 0.94]
McCance 2010	126/375	152/374		13.3 %	0.83 [0.69, 1.00]
Poston 2006	400/1372	373/1376		17.7 %	1.08 [0.95, 1.21]
Spinnato 2007	96/351	82/349		9.9 %	1.16 [0.90, 1.50]
Xu 2010	193/1243	184/1293		13.4 %	1.09 [0.91, 1.31]
Subtotal (95% CI)	**3663**	**3713**		**60.3 %**	**0.99 [0.83, 1.18]**
Total events: 849 (Vitamin E), 836 (Control)					
Heterogeneity: Tau² = 0.03; Chi² = 17.92, df = 7 (P = 0.01); I² =61%					

0.1 0.2   0.5   1   2   5   10

Favours vitamin E   Favours control

(*Continued* . . .)

Study or subgroup	Vitamin E	Control	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			

Test for overall effect: Z = 0.13 (P = 0.89)

Total (95% CI) **10265** **10300** ◆ **100.0 %** **0.98 [0.88, 1.09]**

Total events: 1614 (Vitamin E), 1638 (Control)

Heterogeneity: Tau² = 0.01; Chi² = 20.80, df = 10 (P = 0.02); I² =52%

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Chi² = 1.46, df = 3 (P = 0.69), I² =0.0%

```
     0.1  0.2   0.5    1    2    5   10
     Favours vitamin E    Favours control
```

Analysis 4.5. Comparison 4 Any vitamin E supplementation (subgroup analyses by dietary intake), Outcome 5 Clinical pre-eclampsia (random-effects model).

Review: Vitamin E supplementation in pregnancy

Comparison: 4 Any vitamin E supplementation (subgroup analyses by dietary intake)

Outcome: 5 Clinical pre-eclampsia (random-effects model)

Study or subgroup	Vitamin E	Control	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
1 "Low nutritional status"					
Villar 2009	164/681	157/674	■	14.9 %	1.03 [0.85, 1.25]
Subtotal (95% CI)	**681**	**674**	◆	**14.9 %**	**1.03 [0.85, 1.25]**
Total events: 164 (Vitamin E), 157 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					
2 Low baseline vitamin E status (≤ 5 mol/mmol cholesterol)					
McCance 2010 (1)	4/51	10/44	├──	1.9 %	0.35 [0.12, 1.02]
Subtotal (95% CI)	**51**	**44**	◆	**1.9 %**	**0.35 [0.12, 1.02]**
Total events: 4 (Vitamin E), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.92 (P = 0.055)					
3 Moderate/high baseline antioxidant status (> 5 mol/mmol cholesterol)					

```
   0.001 0.01  0.1    1    10  100  1000
     Favours vitamin E    Favours control
```

(*Continued* . . .)

Study or subgroup	Vitamin E	Control	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
McCance 2010	41/281	55/291		9.3 %	0.77 [0.53, 1.12]
Subtotal (95% CI)	**281**	**291**		**9.3 %**	**0.77 [0.53, 1.12]**
Total events: 41 (Vitamin E), 55 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
4 Low dietary intake					
Rumbold 2006	56/935	47/942		9.1 %	1.20 [0.82, 1.75]
Subtotal (95% CI)	**935**	**942**		**9.1 %**	**1.20 [0.82, 1.75]**
Total events: 56 (Vitamin E), 47 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					
5 Adequate dietary intake					
Roberts 2010	358/4993	332/4976		16.4 %	1.07 [0.93, 1.24]
Subtotal (95% CI)	**4993**	**4976**		**16.4 %**	**1.07 [0.93, 1.24]**
Total events: 358 (Vitamin E), 332 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
6 Dietary intake unclear					
Beazley 2005	9/52	9/48		3.0 %	0.92 [0.40, 2.13]
Chappell 1999	11/141	24/142		4.2 %	0.46 [0.24, 0.91]
Huria 2010	5/107	11/109		2.1 %	0.46 [0.17, 1.29]
Kalpdev 2011	2/22	3/22		0.8 %	0.67 [0.12, 3.61]
Mahdy 2004	1/46	2/67		0.4 %	0.73 [0.07, 7.80]
Nasrolahi 2006	5/290	18/290		2.3 %	0.28 [0.10, 0.74]
Poston 2006	181/1196	187/1199		15.0 %	0.97 [0.80, 1.17]
Rivas 2000	1/63	14/64		0.6 %	0.07 [0.01, 0.54]
Spinnato 2007	49/355	55/352		9.6 %	0.88 [0.62, 1.26]
Xu 2010	69/1167	68/1196		10.5 %	1.04 [0.75, 1.44]
Subtotal (95% CI)	**3439**	**3489**		**48.5 %**	**0.74 [0.56, 0.98]**
Total events: 333 (Vitamin E), 391 (Control)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 18.80, df = 9 (P = 0.03); I^2 =52%					
Test for overall effect: Z = 2.10 (P = 0.036)					
Total (95% CI)	**10380**	**10416**		**100.0 %**	**0.88 [0.76, 1.03]**
Total events: 956 (Vitamin E), 992 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 28.72, df = 14 (P = 0.01); I^2 =51%					
Test for overall effect: Z = 1.54 (P = 0.12)					
Test for subgroup differences: Chi^2 = 11.92, df = 5 (P = 0.04), I^2 =58%					

0.001 0.01 0.1   1   10   100   1000

Favours vitamin E   Favours control

(1) Blood samples were not available for all women in this trial, therefore the denominators are different to those reported in the overall comparison in graph 1.10.

Analysis 4.6.   Comparison 4 Any vitamin E supplementation (subgroup analyses by dietary intake), Outcome 6 Intrauterine growth restriction (less than third centile or the most extreme centile reported).

Review: Vitamin E supplementation in pregnancy

Comparison: 4 Any vitamin E supplementation (subgroup analyses by dietary intake)

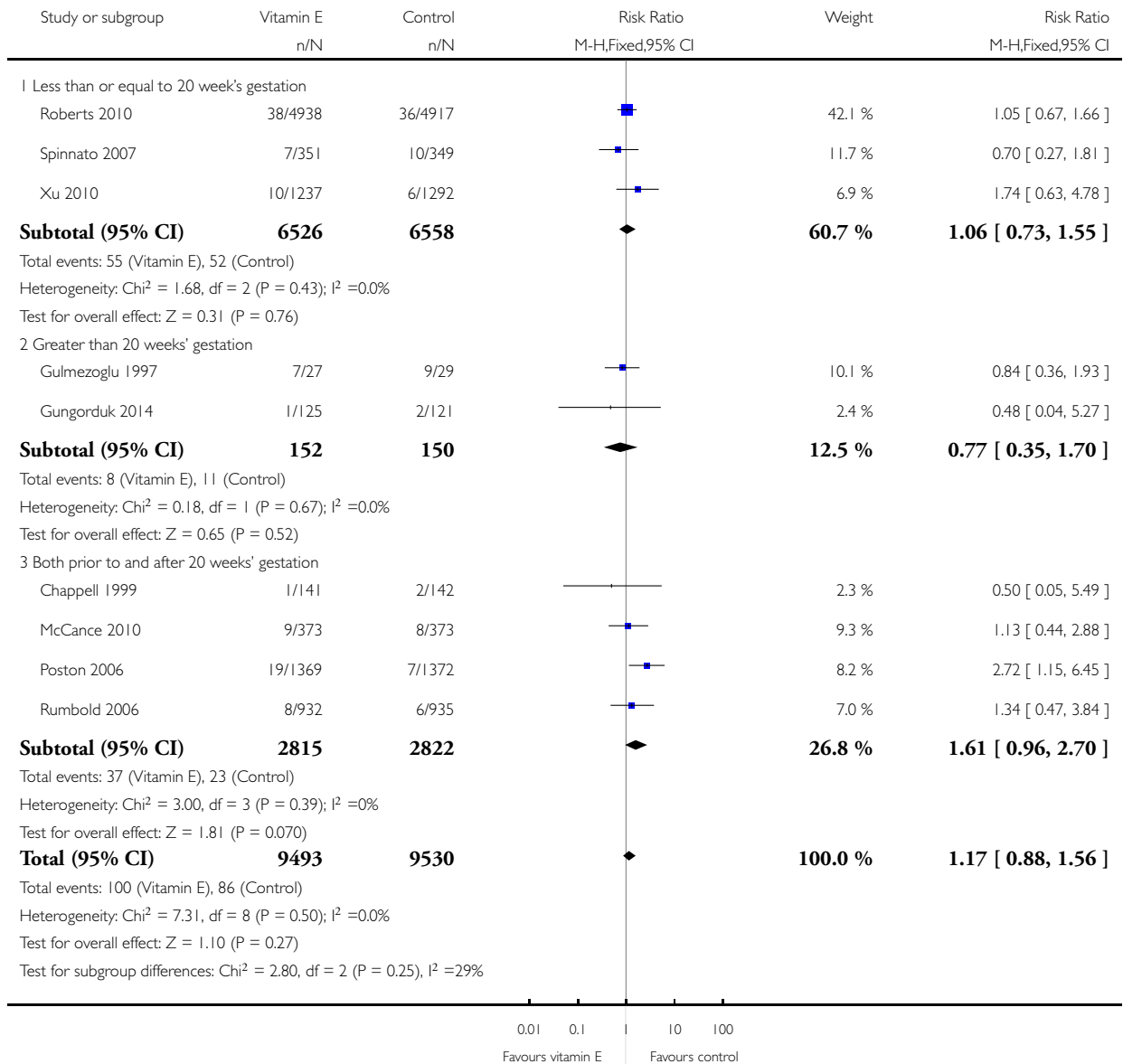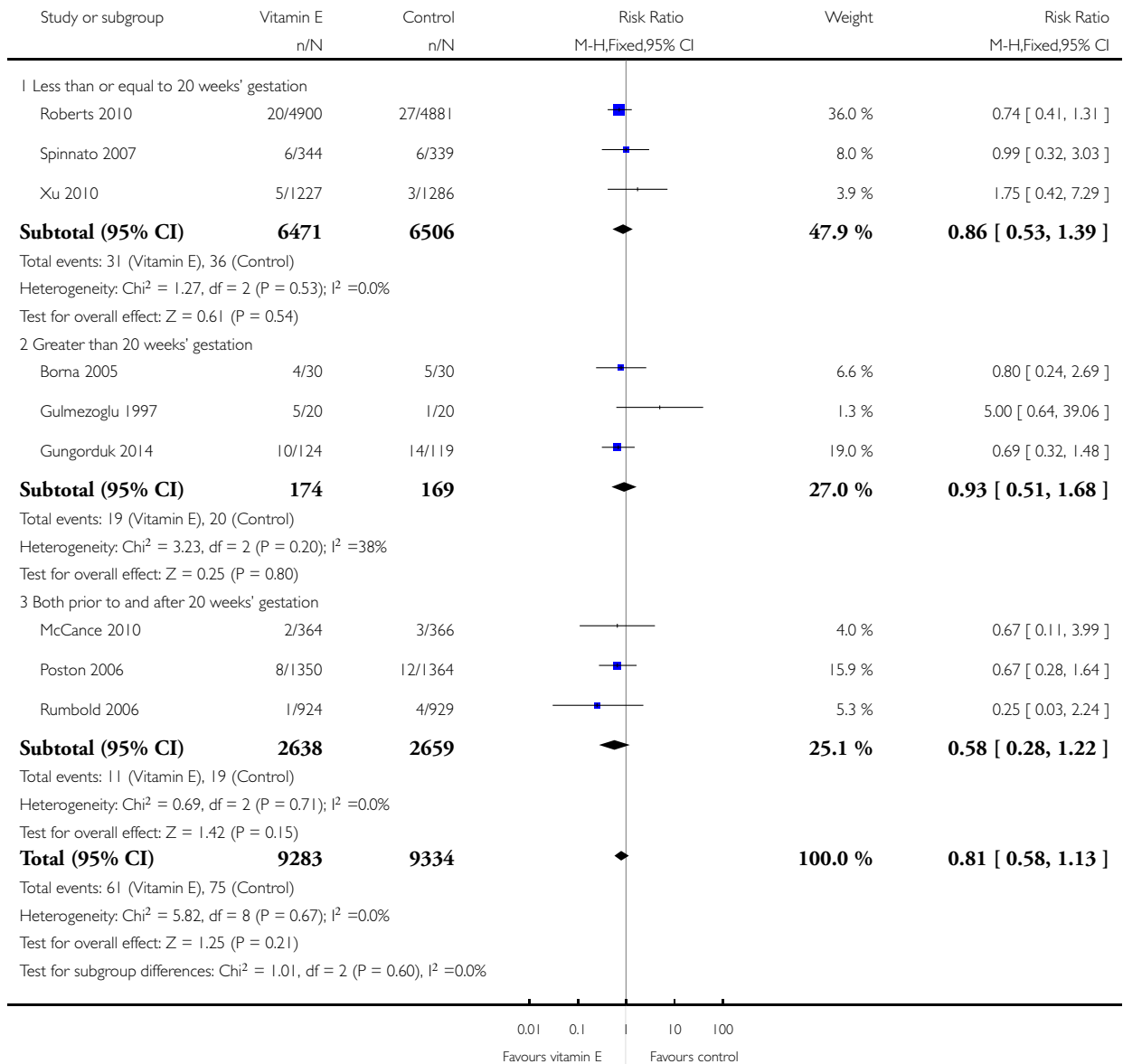Outcome: 6 Intrauterine growth restriction (less than third centile or the most extreme centile reported)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 "Low nutritional status"					
Villar 2009	141/592	149/573		14.1 %	0.92 [0.75, 1.12]
Subtotal (95% CI)	**592**	**573**		**14.1 %**	**0.92 [0.75, 1.12]**
Total events: 141 (Vitamin E), 149 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					
2 Low dietary intake					
Rumbold 2006	80/924	92/929		8.5 %	0.87 [0.66, 1.16]
Subtotal (95% CI)	**924**	**929**		**8.5 %**	**0.87 [0.66, 1.16]**
Total events: 80 (Vitamin E), 92 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					
3 Adequate dietary intake					
Roberts 2010	133/4900	132/4881		12.3 %	1.00 [0.79, 1.27]
Subtotal (95% CI)	**4900**	**4881**		**12.3 %**	**1.00 [0.79, 1.27]**
Total events: 133 (Vitamin E), 132 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
4 Dietary intake unclear					
Beazley 2005	2/52	4/48		0.4 %	0.46 [0.09, 2.41]
Chappell 1999	33/141	45/142		4.2 %	0.74 [0.50, 1.08]
Huria 2010	12/107	13/109		1.2 %	0.94 [0.45, 1.97]
Kalpdev 2011	3/22	2/22		0.2 %	1.50 [0.28, 8.12]
McCance 2010	23/373	36/372		3.4 %	0.64 [0.39, 1.05]
Poston 2006	403/1385	360/1386		33.5 %	1.12 [0.99, 1.26]
Spinnato 2007	49/356	49/352		4.6 %	0.99 [0.68, 1.43]
Xu 2010	173/1243	194/1293		17.7 %	0.93 [0.77, 1.12]

0.01   0.1   1   10   100

Favours vitamin E   Favours control

(*Continued* . . .)

Vitamin E supplementation in pregnancy (Review)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**3679**	**3724**		**65.1 %**	**1.00 [0.91, 1.10]**

Total events: 698 (Vitamin E), 703 (Control)

Heterogeneity: Chi² = 10.52, df = 7 (P = 0.16); I² =33%

Test for overall effect: Z = 0.06 (P = 0.95)

| **Total (95% CI)** | **10095** | **10107** | | **100.0 %** | **0.98 [0.91, 1.06]** |

Total events: 1052 (Vitamin E), 1076 (Control)

Heterogeneity: Chi² = 12.06, df = 10 (P = 0.28); I² =17%

Test for overall effect: Z = 0.52 (P = 0.60)

Test for subgroup differences: Chi² = 1.34, df = 3 (P = 0.72), I² =0.0%

```
              0.01   0.1    1    10   100
             Favours vitamin E   Favours control
```

Analysis 5.1. Comparison 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry), Outcome 1 Stillbirth.

Review: Vitamin E supplementation in pregnancy

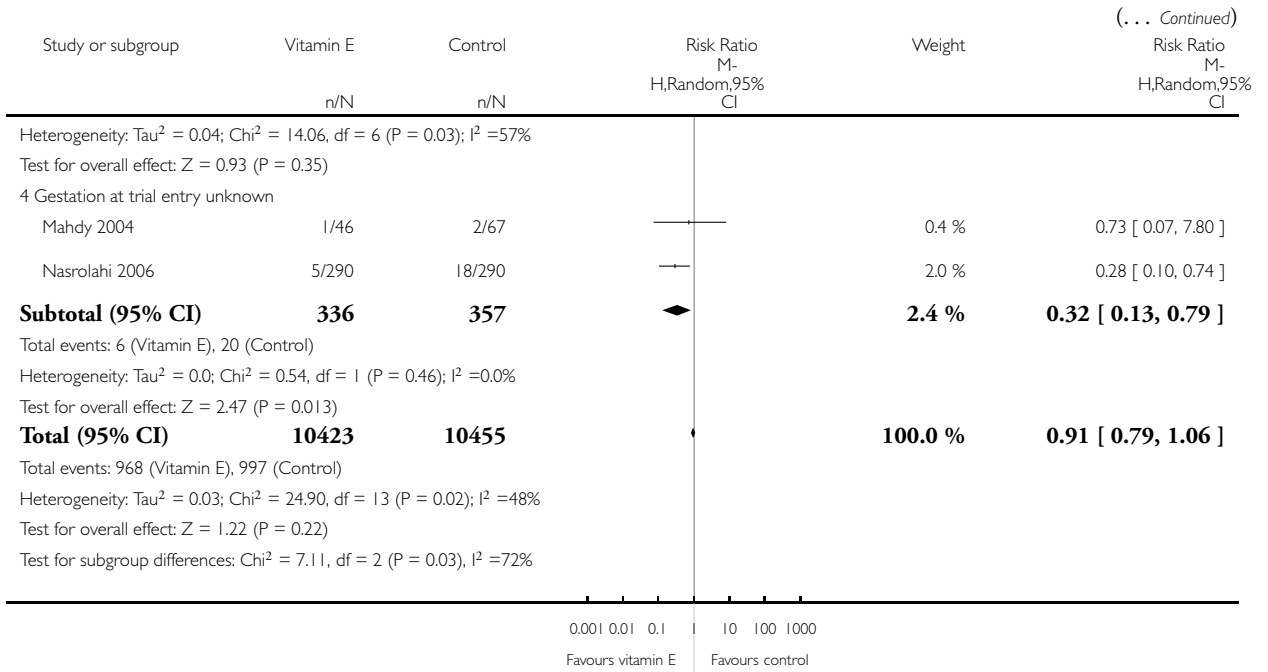Comparison: 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry)

Outcome: 1 Stillbirth

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High/increased risk					
Chappell 1999	1/141	2/142		2.3 %	0.50 [0.05, 5.49]
Gulmezoglu 1997	7/27	9/29		10.1 %	0.84 [0.36, 1.93]
Gungorduk 2014	1/125	2/121		2.4 %	0.48 [0.04, 5.27]
McCance 2010	9/373	8/373		9.3 %	1.13 [0.44, 2.88]
Poston 2006	19/1369	7/1372		8.2 %	2.72 [1.15, 6.45]
Spinnato 2007	7/351	10/349		11.7 %	0.70 [0.27, 1.81]
Xu 2010	10/1237	6/1292		6.9 %	1.74 [0.63, 4.78]
Subtotal (95% CI)	**3623**	**3678**		**50.9 %**	**1.25 [0.85, 1.84]**

Total events: 54 (Vitamin E), 44 (Control)

```
              0.01   0.1    1    10   100
             Favours vitamin E   Favours control
```

(*Continued* . . .)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 7.08, df = 6 (P = 0.31); I² =15%					
Test for overall effect: Z = 1.13 (P = 0.26)					
2 Low/moderate risk					
Roberts 2010	38/4938	36/4917		42.1 %	1.05 [0.67, 1.66]
Rumbold 2006	8/932	6/935		7.0 %	1.34 [0.47, 3.84]
Subtotal (95% CI)	**5870**	**5852**		**49.1 %**	**1.09 [0.72, 1.66]**
Total events: 46 (Vitamin E), 42 (Control)					
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					
Total (95% CI)	**9493**	**9530**		**100.0 %**	**1.17 [0.88, 1.56]**
Total events: 100 (Vitamin E), 86 (Control)					
Heterogeneity: Chi² = 7.31, df = 8 (P = 0.50); I² =0.0%					
Test for overall effect: Z = 1.10 (P = 0.27)					
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² =0.0%					

```
        0.01   0.1    1    10   100
     Favours vitamin E      Favours control
```

Analysis 5.2.   Comparison 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry), Outcome 2 Neonatal death.

Review: Vitamin E supplementation in pregnancy

Comparison: 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry)
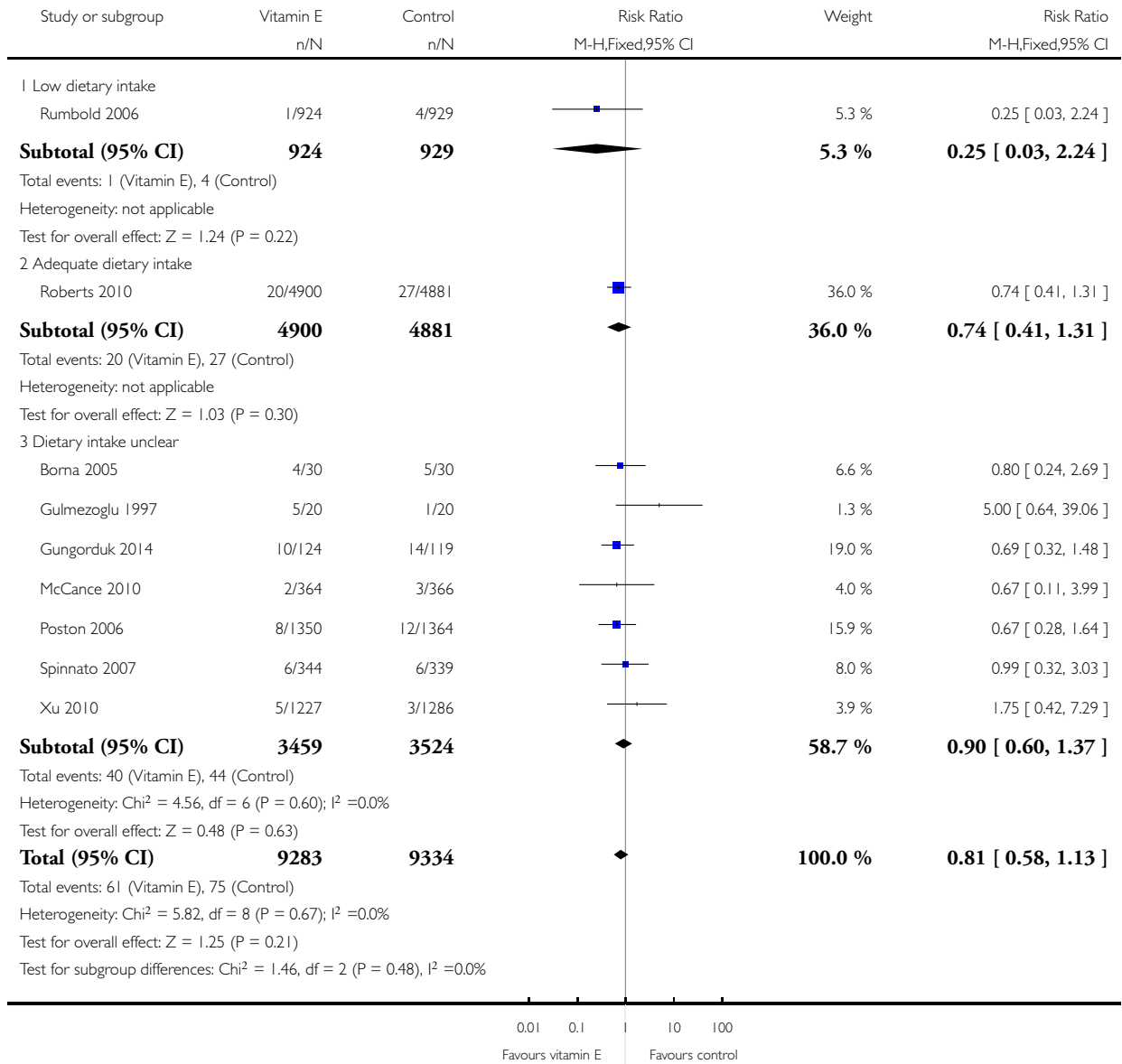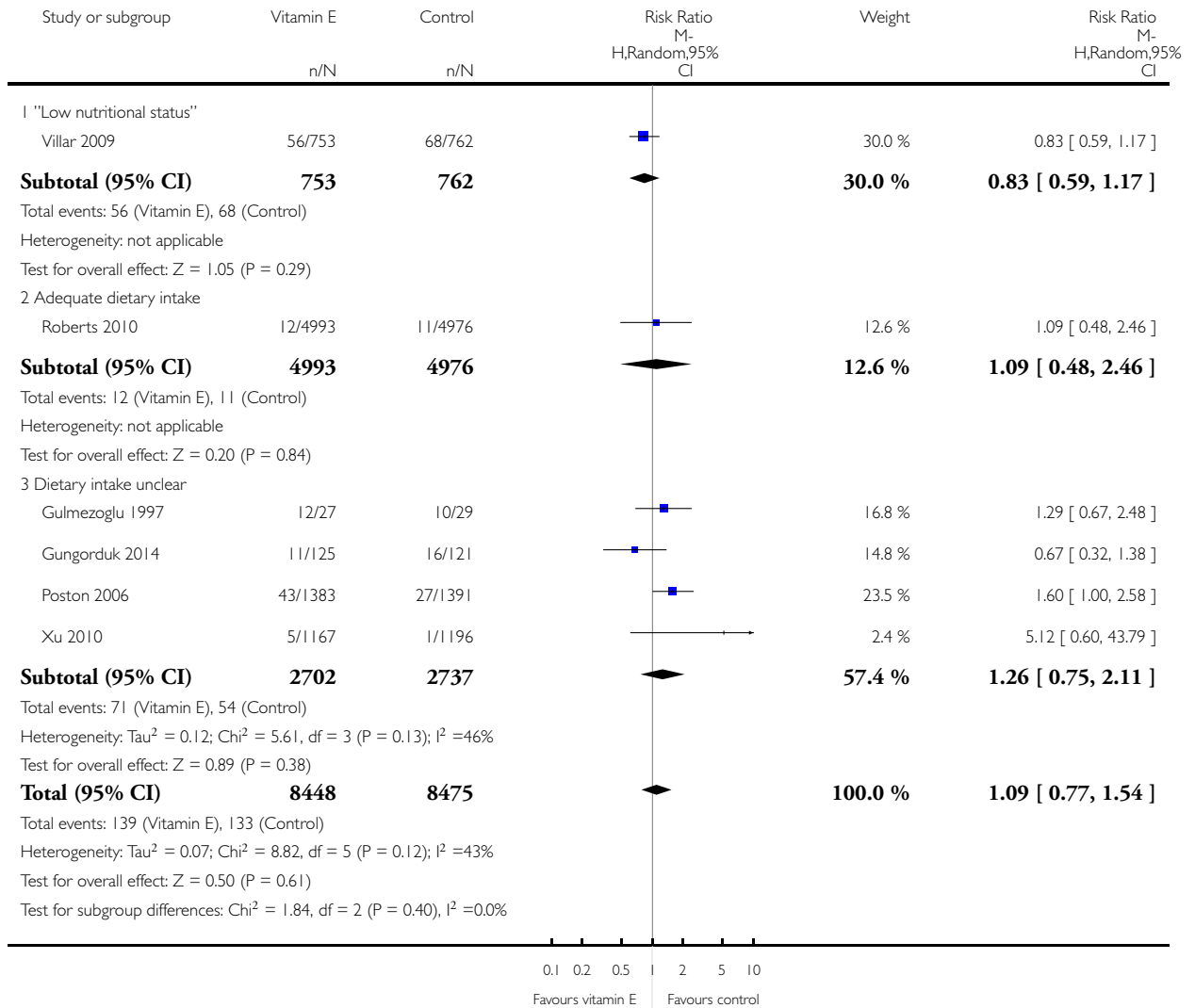
Outcome: 2 Neonatal death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High/increased risk					
Borna 2005	4/30	5/30		6.6 %	0.80 [0.24, 2.69]
Gulmezoglu 1997	5/20	1/20		1.3 %	5.00 [0.64, 39.06]
Gungorduk 2014	10/124	14/119		19.0 %	0.69 [0.32, 1.48]
McCance 2010	2/364	3/366		4.0 %	0.67 [0.11, 3.99]
Poston 2006	8/1350	12/1364		15.9 %	0.67 [0.28, 1.64]
Spinnato 2007	6/344	6/339		8.0 %	0.99 [0.32, 3.03]
Xu 2010	5/1227	3/1286		3.9 %	1.75 [0.42, 7.29]
Subtotal (95% CI)	**3459**	**3524**		**58.7 %**	**0.90 [0.60, 1.37]**
Total events: 40 (Vitamin E), 44 (Control)					
Heterogeneity: Chi² = 4.56, df = 6 (P = 0.60); I² =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
2 Low/moderate risk					
Roberts 2010	20/4900	27/4881		36.0 %	0.74 [0.41, 1.31]
Rumbold 2006	1/924	4/929		5.3 %	0.25 [0.03, 2.24]
Subtotal (95% CI)	**5824**	**5810**		**41.3 %**	**0.68 [0.39, 1.17]**
Total events: 21 (Vitamin E), 31 (Control)					
Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² =0.0%					
Test for overall effect: Z = 1.39 (P = 0.16)					
Total (95% CI)	**9283**	**9334**		**100.0 %**	**0.81 [0.58, 1.13]**
Total events: 61 (Vitamin E), 75 (Control)					
Heterogeneity: Chi² = 5.82, df = 8 (P = 0.67); I² =0.0%					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Chi² = 0.68, df = 1 (P = 0.41), I² =0.0%					

0.01   0.1   1   10   100

Favours vitamin E   Favours control

Analysis 5.3.   Comparison 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry), Outcome 3 Perinatal death.

Review: Vitamin E supplementation in pregnancy

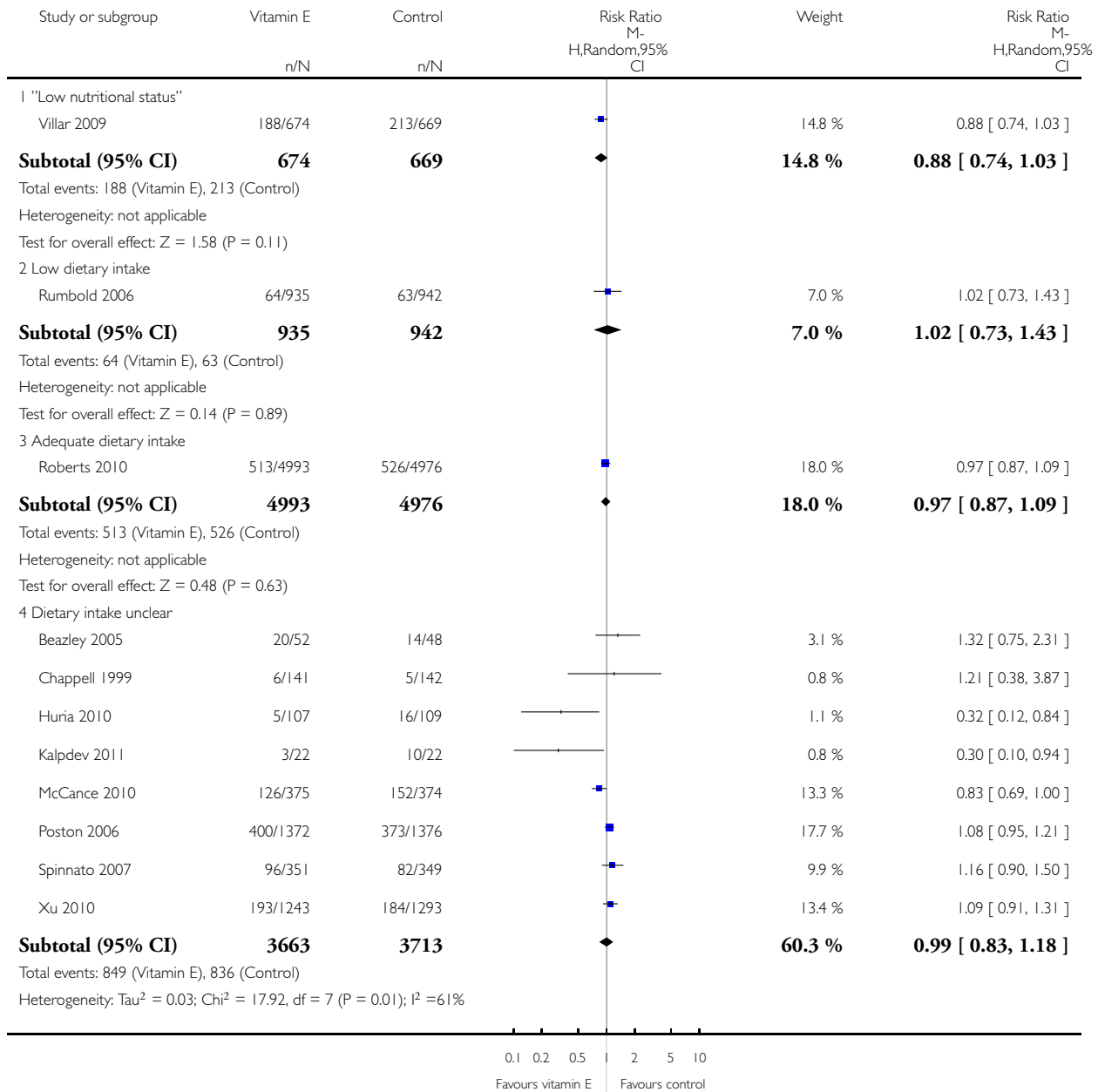Comparison: 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry)

Outcome: 3 Perinatal death

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 High/increased risk					
Gulmezoglu 1997	12/27	10/29		16.8 %	1.29 [0.67, 2.48]
Gungorduk 2014	11/125	16/121		14.8 %	0.67 [0.32, 1.38]
Poston 2006	43/1383	27/1391		23.5 %	1.60 [1.00, 2.58]
Villar 2009	56/753	68/762		30.0 %	0.83 [0.59, 1.17]
Xu 2010	5/1167	1/1196		2.4 %	5.12 [0.60, 43.79]
Subtotal (95% CI)	**3455**	**3499**		**87.4 %**	**1.10 [0.73, 1.67]**
Total events: 127 (Vitamin E), 122 (Control)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 8.81, df = 4 (P = 0.07); I^2 =55%					
Test for overall effect: Z = 0.47 (P = 0.64)					
2 Low/moderate risk					
Roberts 2010	12/4993	11/4976		12.6 %	1.09 [0.48, 2.46]
Subtotal (95% CI)	**4993**	**4976**		**12.6 %**	**1.09 [0.48, 2.46]**
Total events: 12 (Vitamin E), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
Total (95% CI)	**8448**	**8475**		**100.0 %**	**1.09 [0.77, 1.54]**
Total events: 139 (Vitamin E), 133 (Control)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 8.82, df = 5 (P = 0.12); I^2 =43%					
Test for overall effect: Z = 0.50 (P = 0.61)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.97), I^2 =0.0%					

0.1   0.2   0.5   1   2   5   10

Favours vitamin E   Favours control

Analysis 5.4. Comparison 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry), Outcome 4 Preterm birth (less than 37 weeks' gestation).

Review: Vitamin E supplementation in pregnancy

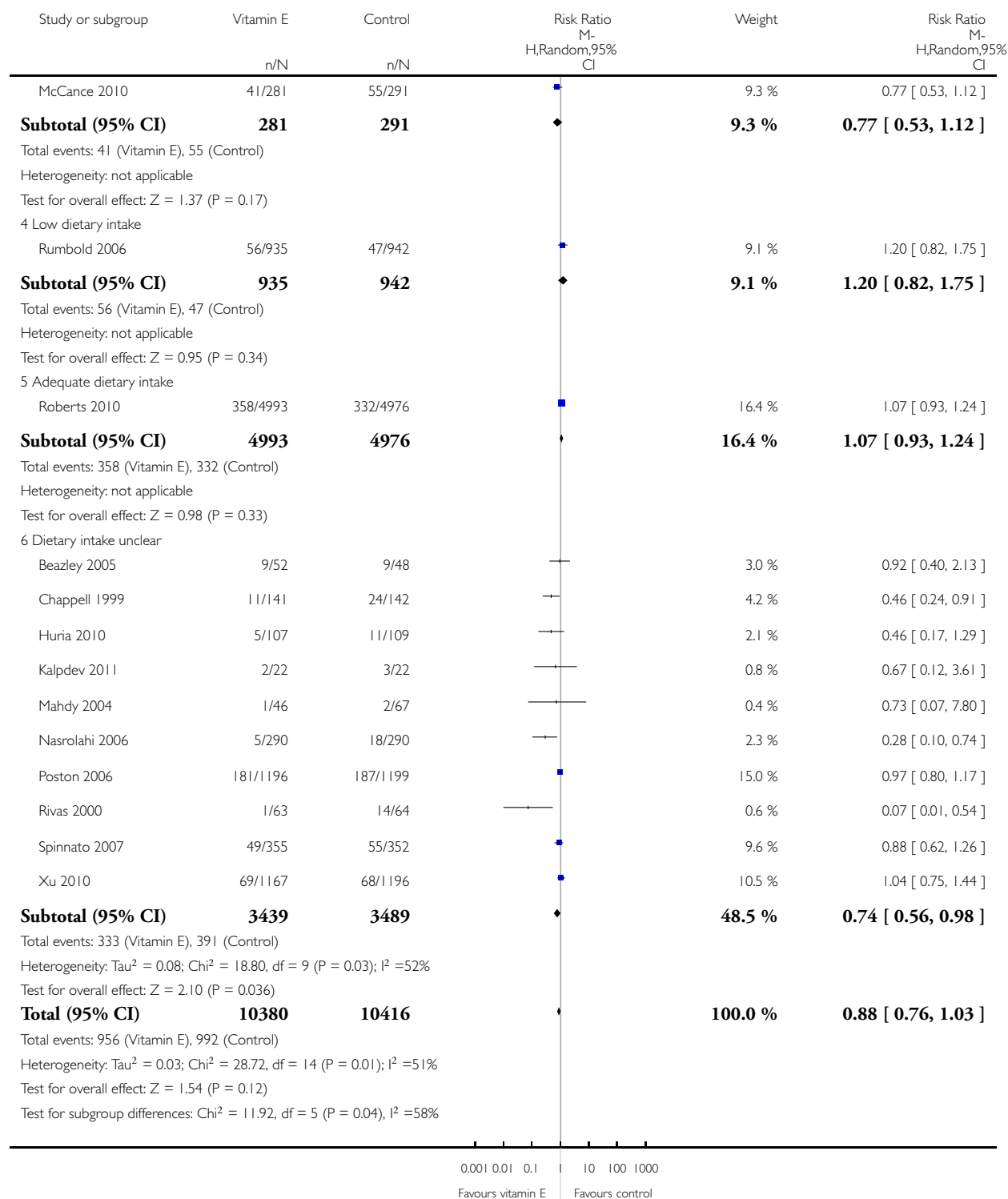Comparison: 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry)

Outcome: 4 Preterm birth (less than 37 weeks' gestation)

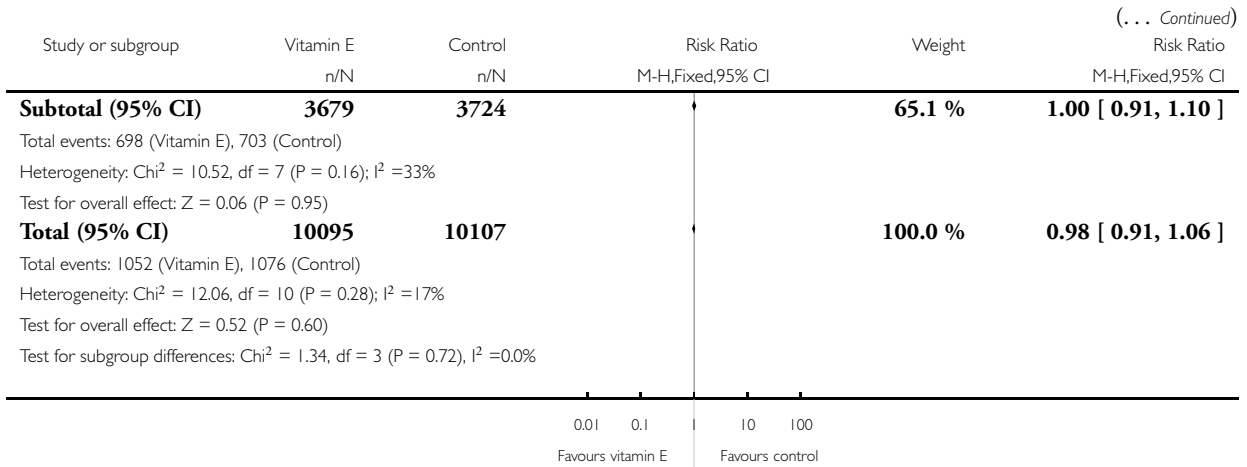| Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 High/increased risk					
Beazley 2005	20/52	14/48		3.1 %	1.32 [0.75, 2.31]
Chappell 1999	6/141	5/142		0.8 %	1.21 [0.38, 3.87]
Kalpdev 2011	3/22	10/22		0.8 %	0.30 [0.10, 0.94]
McCance 2010	126/375	152/374		13.3 %	0.83 [0.69, 1.00]
Poston 2006	400/1372	373/1376		17.7 %	1.08 [0.95, 1.21]
Spinnato 2007	96/351	82/349		9.9 %	1.16 [0.90, 1.50]
Villar 2009	188/674	213/669		14.8 %	0.88 [0.74, 1.03]
Xu 2010	193/1243	184/1293		13.4 %	1.09 [0.91, 1.31]
Subtotal (95% CI)	**4230**	**4273**		**73.9 %**	**0.99 [0.87, 1.13]**
Total events: 1032 (Vitamin E), 1033 (Control)					
Heterogeneity: Tau² = 0.02; Chi² = 15.36, df = 7 (P = 0.03); I² =54%					
Test for overall effect: Z = 0.10 (P = 0.92)					
2 Low/moderate risk					
Huria 2010	5/107	16/109		1.1 %	0.32 [0.12, 0.84]
Roberts 2010	513/4993	526/4976		18.0 %	0.97 [0.87, 1.09]
Rumbold 2006	64/935	63/942		7.0 %	1.02 [0.73, 1.43]
Subtotal (95% CI)	**6035**	**6027**		**26.1 %**	**0.89 [0.64, 1.23]**
Total events: 582 (Vitamin E), 605 (Control)					
Heterogeneity: Tau² = 0.05; Chi² = 5.18, df = 2 (P = 0.08); I² =61%					
Test for overall effect: Z = 0.69 (P = 0.49)					
Total (95% CI)	**10265**	**10300**		**100.0 %**	**0.98 [0.88, 1.09]**
Total events: 1614 (Vitamin E), 1638 (Control)					
Heterogeneity: Tau² = 0.01; Chi² = 20.80, df = 10 (P = 0.02); I² =52%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.55), I² =0.0%					

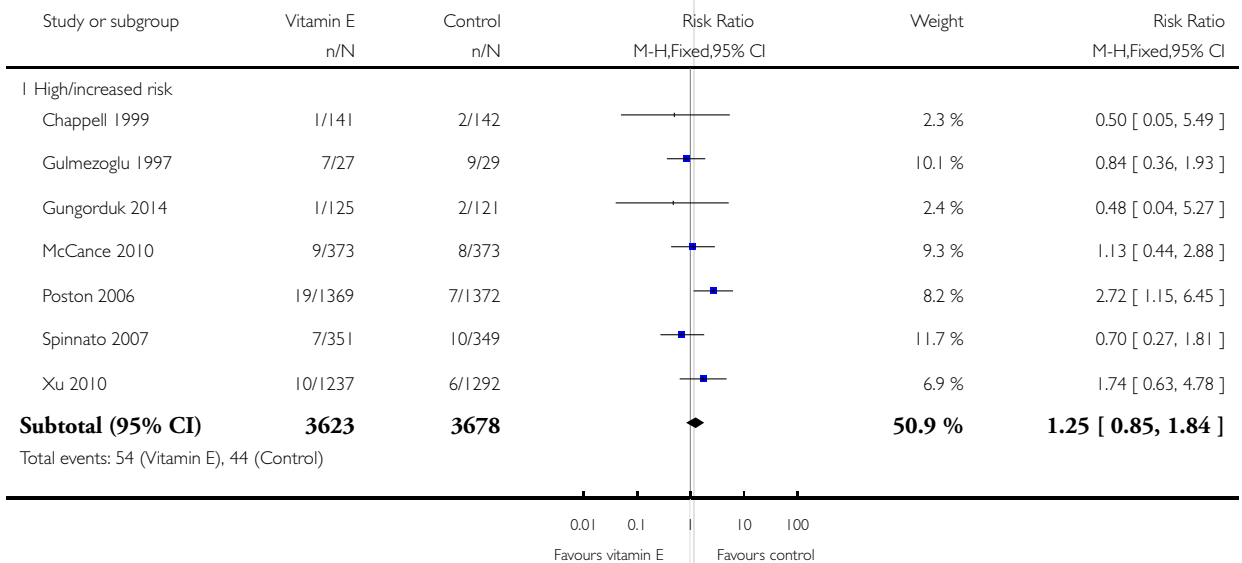0.1 0.2 0.5 1 2 5 10

Favours vitamin E   Favours control

Analysis 5.5. Comparison 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry), Outcome 5 Clinical pre-eclampsia (random-effects model).
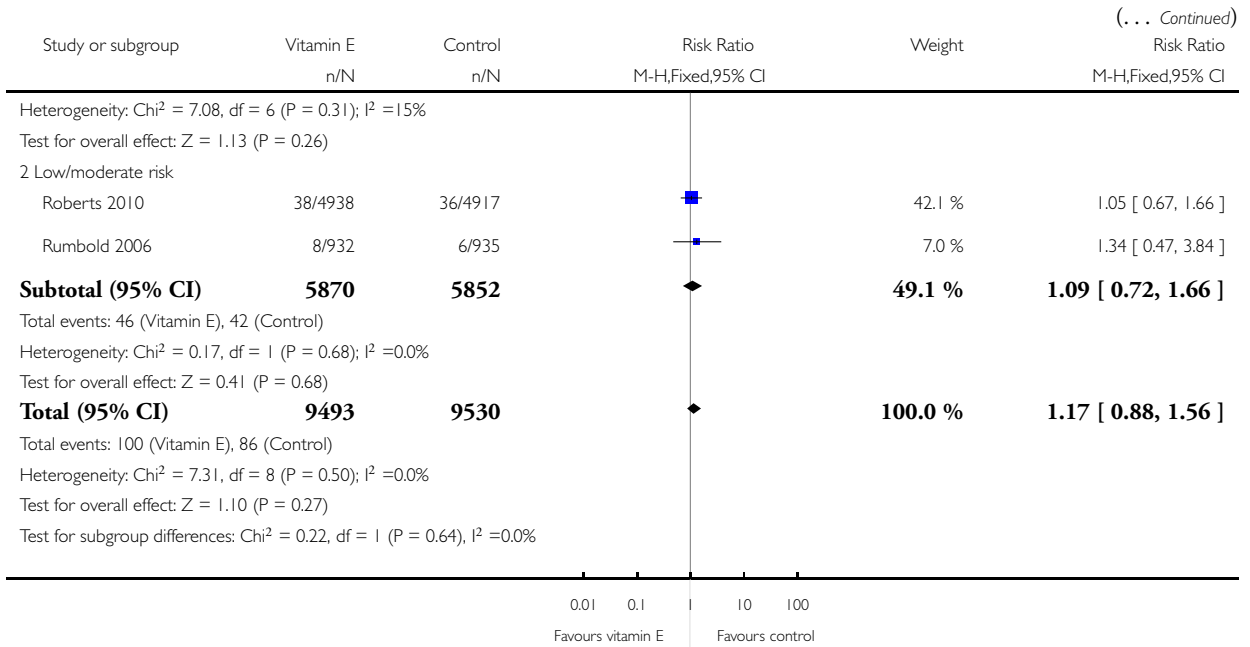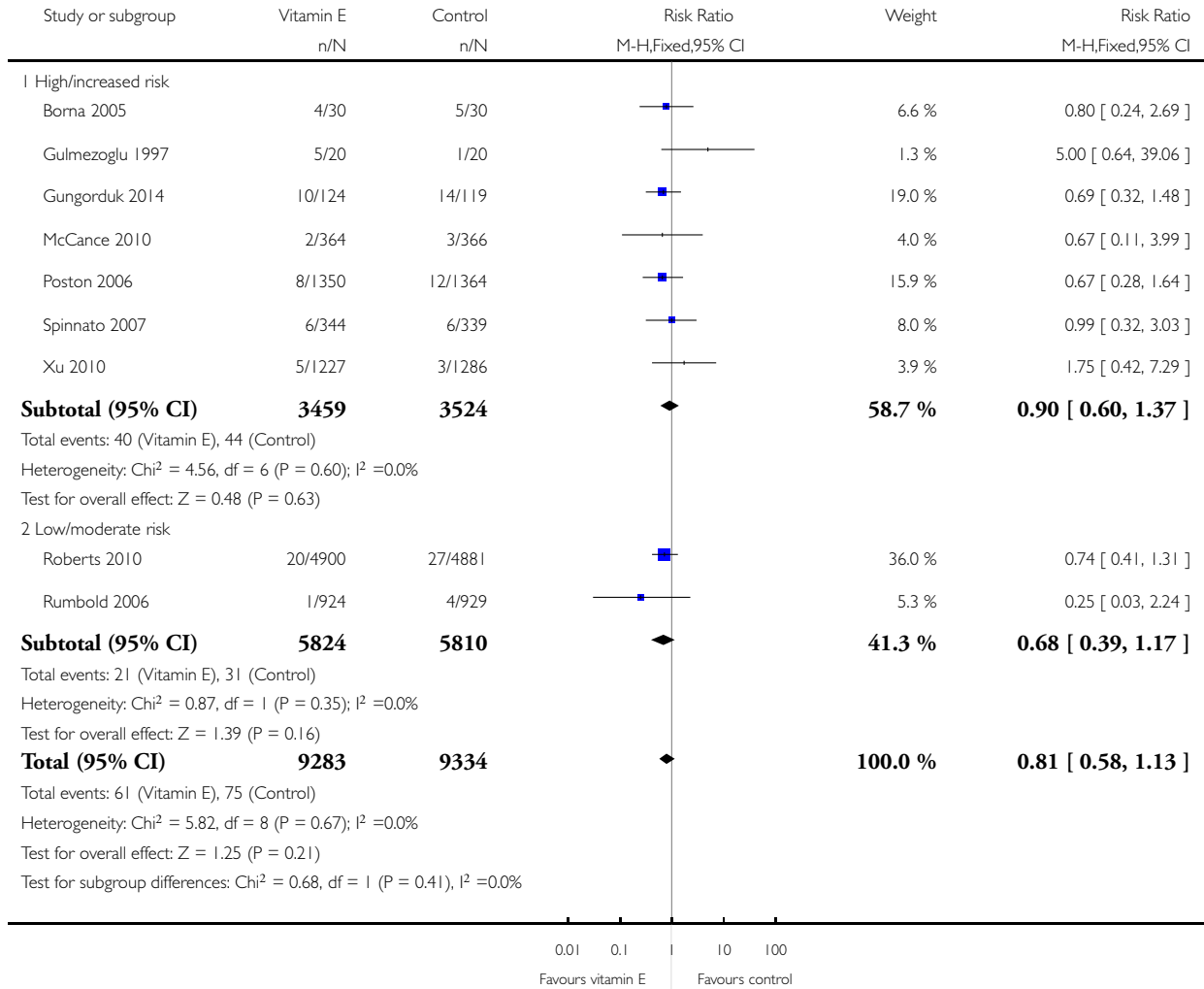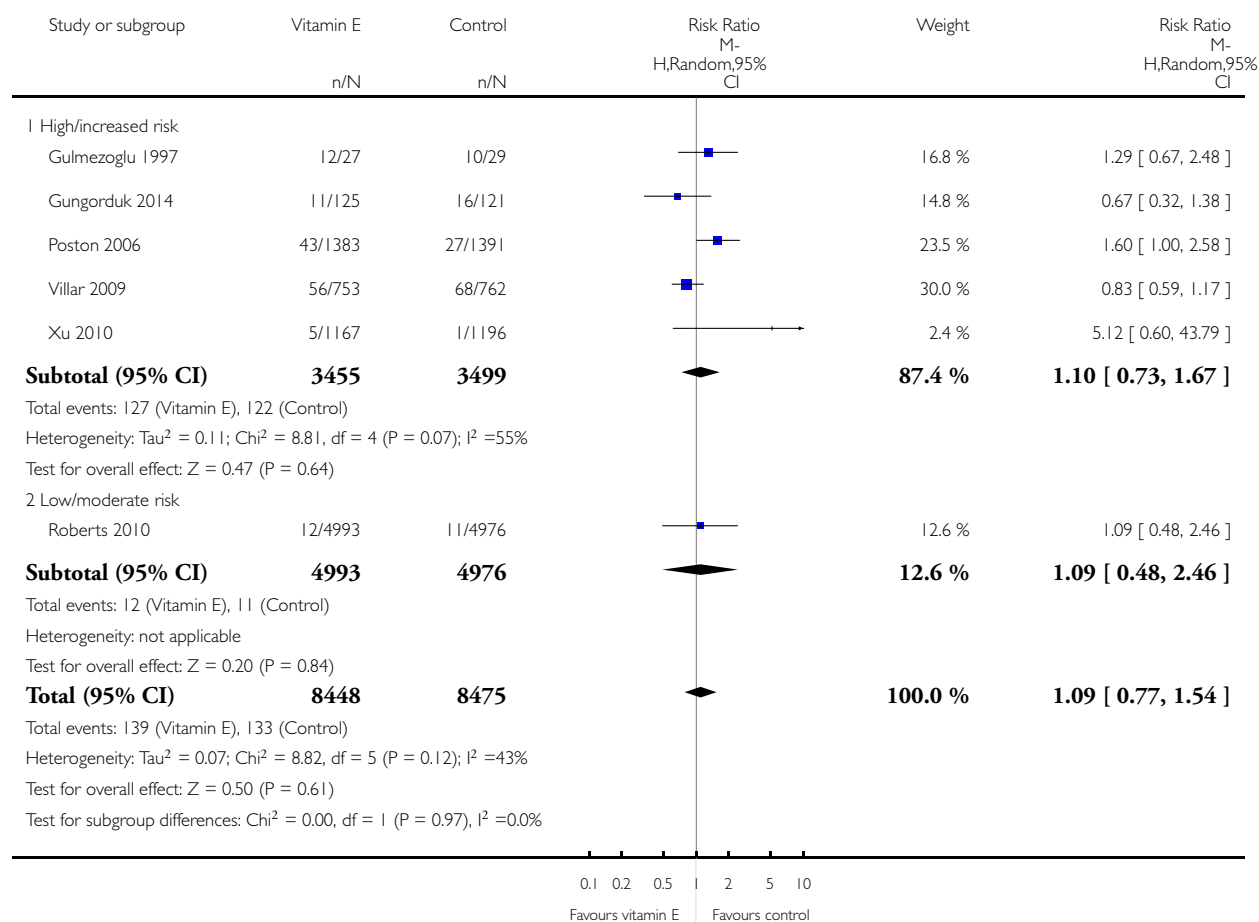
Review: Vitamin E supplementation in pregnancy

Comparison: 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry)

Outcome: 5 Clinical pre-eclampsia (random-effects model)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
1 High/increased risk					
Beazley 2005	9/52	9/48		2.7 %	0.92 [0.40, 2.13]
Chappell 1999	11/141	24/142		3.9 %	0.46 [0.24, 0.91]
Kalpdev 2011	2/22	3/22		0.7 %	0.67 [0.12, 3.61]
McCance 2010	57/375	70/374		10.6 %	0.81 [0.59, 1.12]
Poston 2006	181/1196	187/1199		15.6 %	0.97 [0.80, 1.17]
Rivas 2000	1/63	14/64		0.5 %	0.07 [0.01, 0.54]
Spinnato 2007	49/355	55/352		9.4 %	0.88 [0.62, 1.26]
Villar 2009	164/681	157/674		15.5 %	1.03 [0.85, 1.25]
Xu 2010	69/1167	68/1196		10.4 %	1.04 [0.75, 1.44]
Subtotal (95% CI)	**4052**	**4071**		**69.4 %**	**0.90 [0.76, 1.06]**
Total events: 543 (Vitamin E), 587 (Control)					
Heterogeneity: Tau² = 0.02; Chi² = 13.22, df = 8 (P = 0.10); I² =39%					
Test for overall effect: Z = 1.24 (P = 0.21)					
2 Low/moderate risk					
Huria 2010	5/107	11/109		1.9 %	0.46 [0.17, 1.29]
Mahdy 2004	1/46	2/67		0.4 %	0.73 [0.07, 7.80]
Nasrolahi 2006	5/290	18/290		2.0 %	0.28 [0.10, 0.74]
Roberts 2010	358/4993	332/4976		17.5 %	1.07 [0.93, 1.24]
Rumbold 2006	56/935	47/942		8.8 %	1.20 [0.82, 1.75]
Subtotal (95% CI)	**6371**	**6384**		**30.6 %**	**0.84 [0.56, 1.27]**
Total events: 425 (Vitamin E), 410 (Control)					
Heterogeneity: Tau² = 0.10; Chi² = 10.27, df = 4 (P = 0.04); I² =61%					
Test for overall effect: Z = 0.82 (P = 0.41)					
Total (95% CI)	**10423**	**10455**		**100.0 %**	**0.91 [0.79, 1.06]**
Total events: 968 (Vitamin E), 997 (Control)					
Heterogeneity: Tau² = 0.03; Chi² = 24.90, df = 13 (P = 0.02); I² =48%					
Test for overall effect: Z = 1.22 (P = 0.22)					
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² =0.0%					

0.001 0.01 0.1   1   10 100 1000
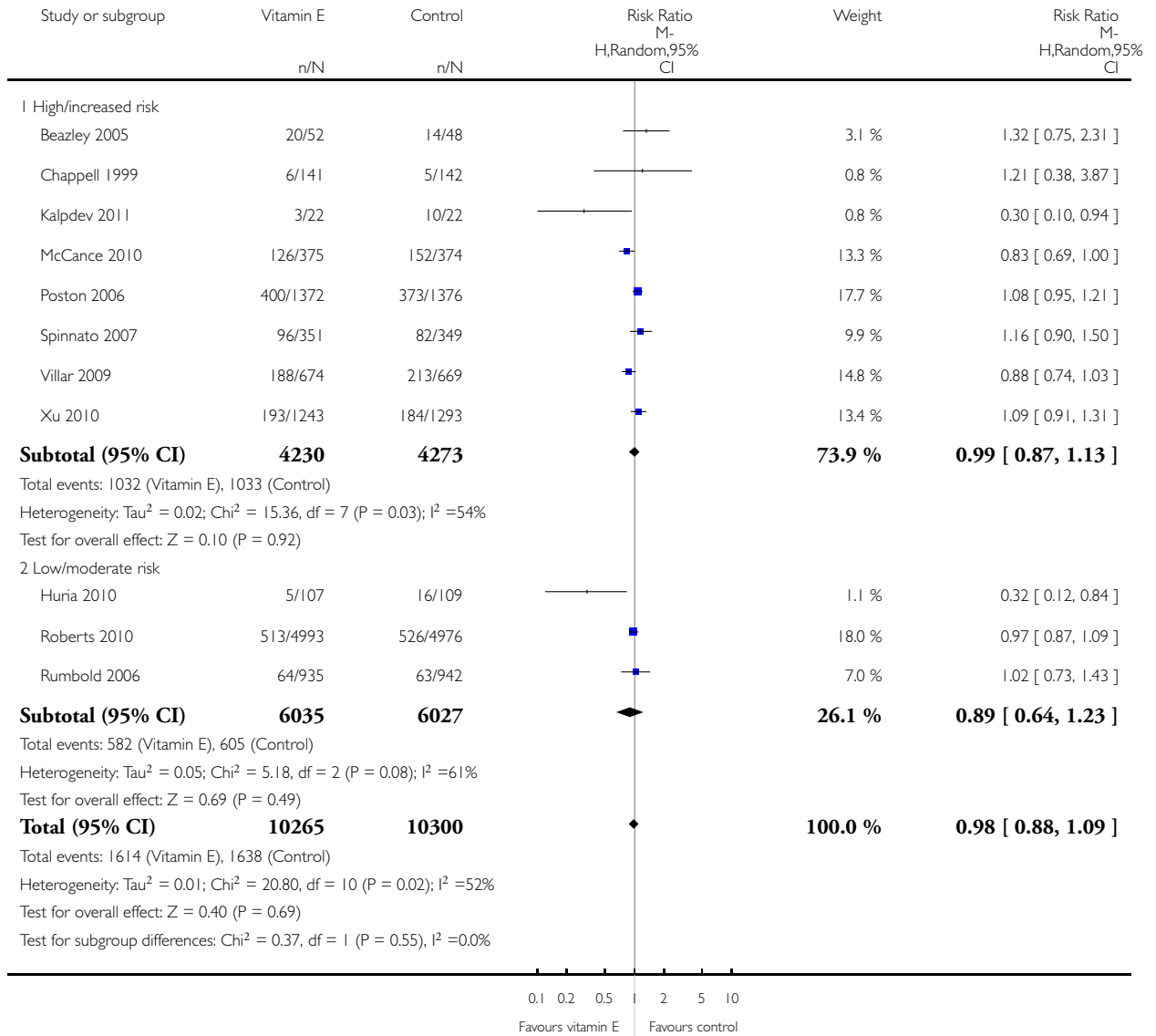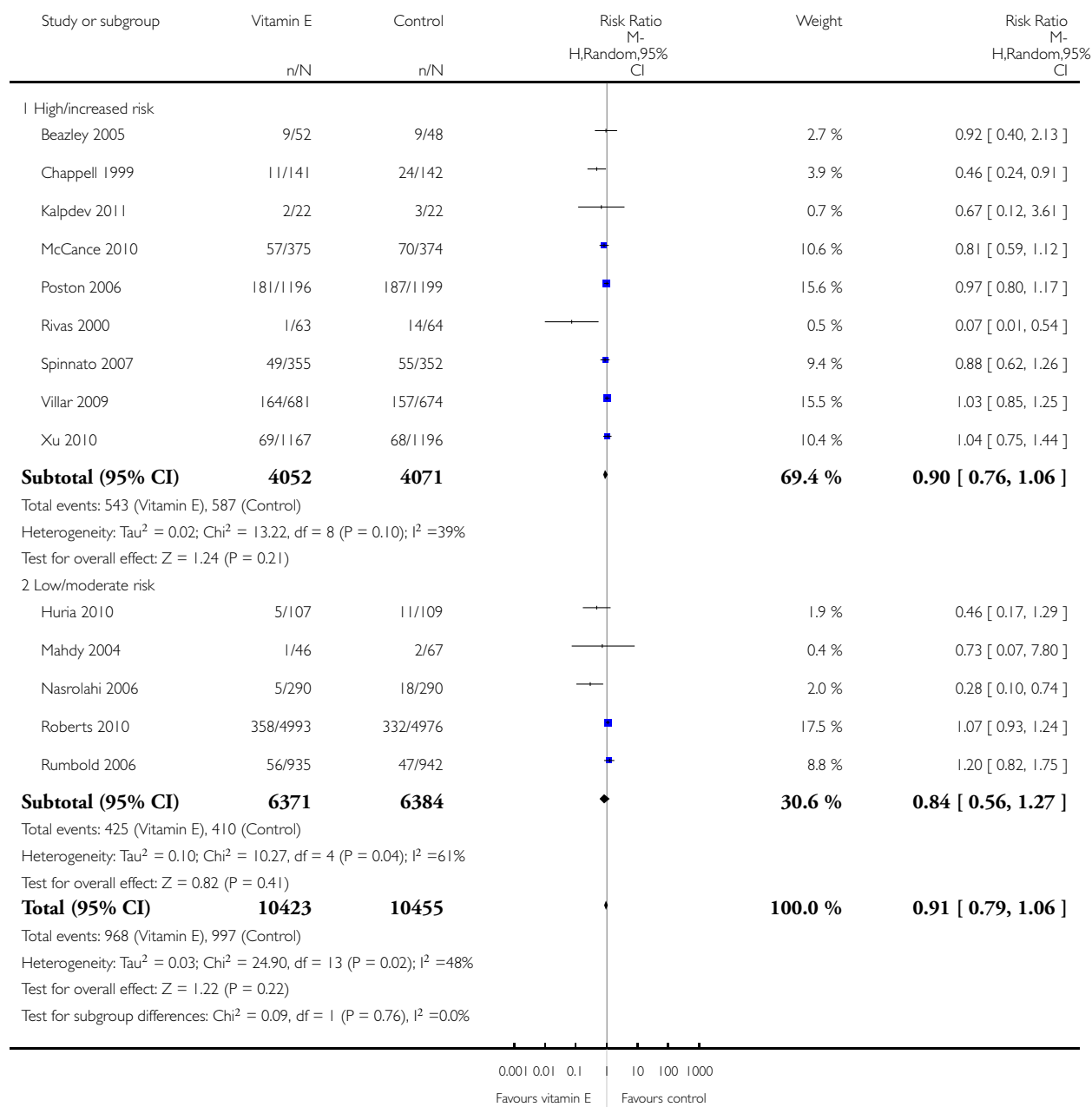
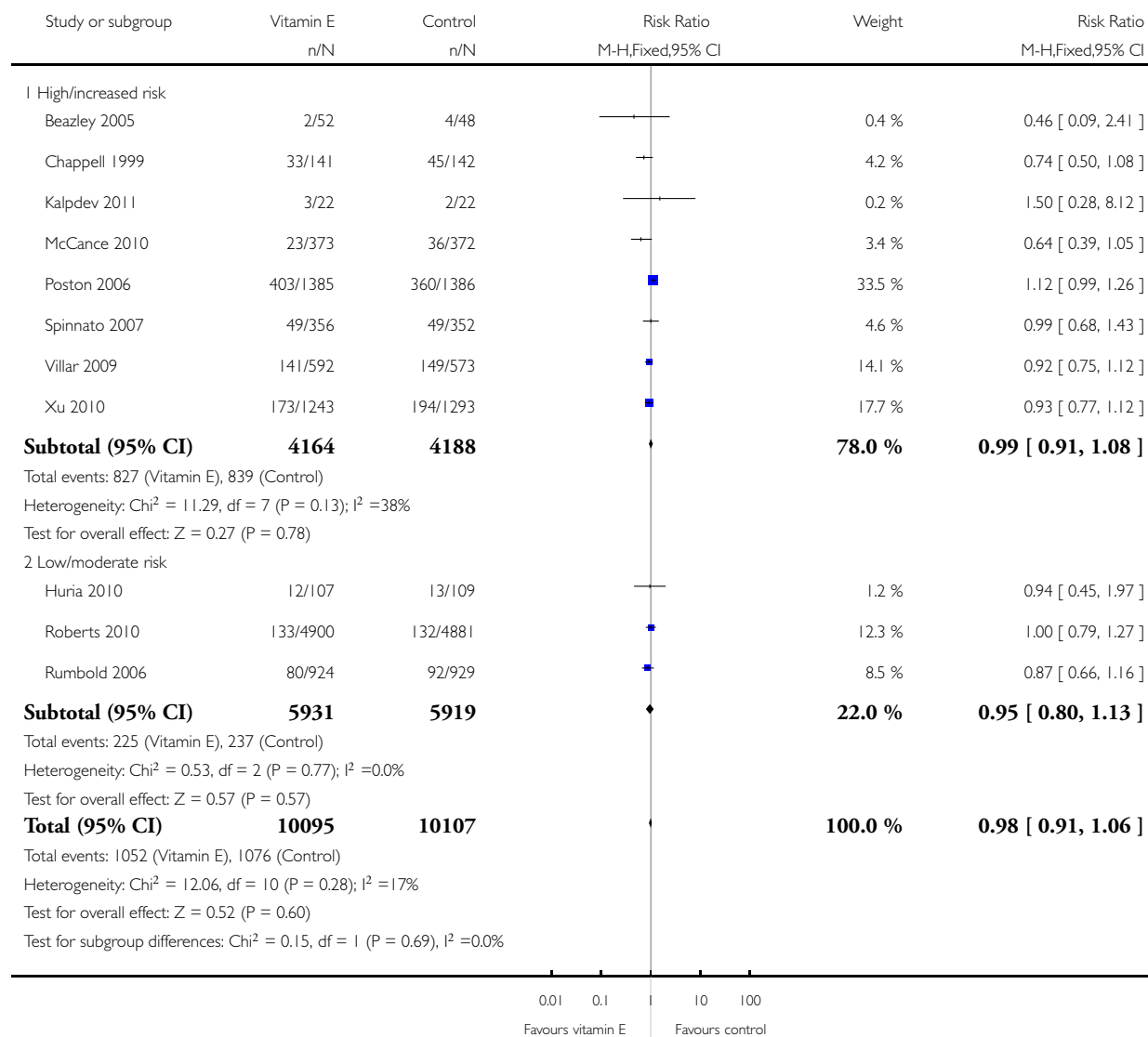Favours vitamin E   Favours control

Analysis 5.6. Comparison 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry), Outcome 6 Intrauterine growth restriction (less than third centile or the most extreme centile reported).

Review: Vitamin E supplementation in pregnancy

Comparison: 5 Any vitamin E supplementation (subgroup analyses by risk of adverse pregnancy outcomes at trial entry)

Outcome: 6 Intrauterine growth restriction (less than third centile or the most extreme centile reported)

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High/increased risk					
Beazley 2005	2/52	4/48		0.4 %	0.46 [0.09, 2.41]
Chappell 1999	33/141	45/142		4.2 %	0.74 [0.50, 1.08]
Kalpdev 2011	3/22	2/22		0.2 %	1.50 [0.28, 8.12]
McCance 2010	23/373	36/372		3.4 %	0.64 [0.39, 1.05]
Poston 2006	403/1385	360/1386		33.5 %	1.12 [0.99, 1.26]
Spinnato 2007	49/356	49/352		4.6 %	0.99 [0.68, 1.43]
Villar 2009	141/592	149/573		14.1 %	0.92 [0.75, 1.12]
Xu 2010	173/1243	194/1293		17.7 %	0.93 [0.77, 1.12]
Subtotal (95% CI)	**4164**	**4188**		**78.0 %**	**0.99 [0.91, 1.08]**
Total events: 827 (Vitamin E), 839 (Control)					
Heterogeneity: Chi² = 11.29, df = 7 (P = 0.13); I² =38%					
Test for overall effect: Z = 0.27 (P = 0.78)					
2 Low/moderate risk					
Huria 2010	12/107	13/109		1.2 %	0.94 [0.45, 1.97]
Roberts 2010	133/4900	132/4881		12.3 %	1.00 [0.79, 1.27]
Rumbold 2006	80/924	92/929		8.5 %	0.87 [0.66, 1.16]
Subtotal (95% CI)	**5931**	**5919**		**22.0 %**	**0.95 [0.80, 1.13]**
Total events: 225 (Vitamin E), 237 (Control)					
Heterogeneity: Chi² = 0.53, df = 2 (P = 0.77); I² =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					
Total (95% CI)	**10095**	**10107**		**100.0 %**	**0.98 [0.91, 1.06]**
Total events: 1052 (Vitamin E), 1076 (Control)					
Heterogeneity: Chi² = 12.06, df = 10 (P = 0.28); I² =17%					
Test for overall effect: Z = 0.52 (P = 0.60)					
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.69), I² =0.0%					

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          0.01    0.1       1      10     100
            Favours vitamin E    Favours control
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APPENDICES

Appendix 1. Search strategy

In the previous version of the review ([Rumbold 2005](#)), authors searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2004, Issue 2), MEDLINE (1966 to May 2004), Current Contents (1998 to May 2004) and EMBASE (1980 to May 2004) for potentially eligible studies:

CENTRAL (*The Cochrane Library* 2004, Issue 2)

pregnan*, vitamin*, tocopher*.

MEDLINE (1966 to May 2004), Current Contents (1998 to May 2004) and EMBASE (1980 to May 2004):

1. vitam*
2. tocopherol*
3. alpha-tocopherol*
4. pregnan*
5. #4 and (#1 or #2 or #3)
6. random*
7. controlled-clinical-trial
8. #6 or #7
9. #5 and #8

WHAT'S NEW

Date	Event	Description
22 March 2016	Amended	Added external source of support for Erika Ota (the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, World Health Organization)

HISTORY

Date	Event	Description
8 April 2015	New citation required and conclusions have changed	There are now data available for over 21,000 women assessing the effects of vitamin E supplementation in combination with other supplements including vitamin C in pregnancy. The new data do not support routine vitamin E supplementation in combination with other agents for the prevention of stillbirth, neonatal death, preterm birth,

		pre-eclampsia, prelabour rupture of membranes or poor fetal growth. Supplementation was associated with a reduced risk of placental abruption. There was some evidence of harm, as vitamin E supplementation appeared to increase the risk of term prelabour rupture of membranes and self-reported abdominal pain. There were no clear differing patterns in the effects of vitamin E supplementation in subgroups of women based on the timing of commencement of supplementation or baseline risk of adverse pregnancy outcomes
8 April 2015	New search has been performed	Search updated and 27 trials identified, of these, 21 were eligible for inclusion. Four trials did not report any clinical outcomes and therefore do not contribute data to the review (in the previous version of the review, three of these trials were excluded).The methods, results and discussion have been updated, new subgroup analyses were undertaken and a 'Summary of findings' table added
29 August 2011	New search has been performed	Data on stillbirth and perinatal death added for 5 new eligible studies, in order to be used in the review "Interventions for preventing stillbirth during pregnancy: an overview of Cochrane systematic reviews"
7 May 2010	Amended	Search updated. Twenty-three new reports added to Studies awaiting classification.
7 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Alice Rumbold developed and wrote the protocol, extracted data, assessed risk of bias and wrote the review. Caroline Crowther commented on and revised the various drafts of the protocol, extracted data and commented on all drafts of the review. Erika Ota, Hiroyuki Hori, and Celine Myazaki assessed eligible studies, extracted data, assessed risk of bias and developed the 'Summary of findings' table.

DECLARATIONS OF INTEREST

Caroline Crowther and Alice Rumbold are Investigators on one of the included trials (Rumbold 2006). Decision about inclusion of this trial and extraction of data about this trial was undertaken by Erika Ota, Hiroyuki Hori and Celine Miyazaki.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, The University of Adelaide, Australia.
- National Centre for Child Health and Development 27B-10, 26A-5, Japan.

External sources

- Japan Agency for Medical Research and development, Japan.
AMED No.27300101
- National Health and Medical Research Council, Australia.
Funding for the PCG Australian and New Zealand Satellite
- The Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, World Health
Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods updated to current standard text for Cochrane Pregnancy and Childbirth. A 'Summary of findings' table has been incorporated.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements [adverse effects]; Antioxidants [*administration & dosage; adverse effects]; Infant, Small for Gestational Age; Pre-Eclampsia [*prevention & control]; Pregnancy Complications [prevention & control]; Pregnancy Outcome; Randomized Controlled Trials as Topic; Vitamin E [*administration & dosage; adverse effects]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy