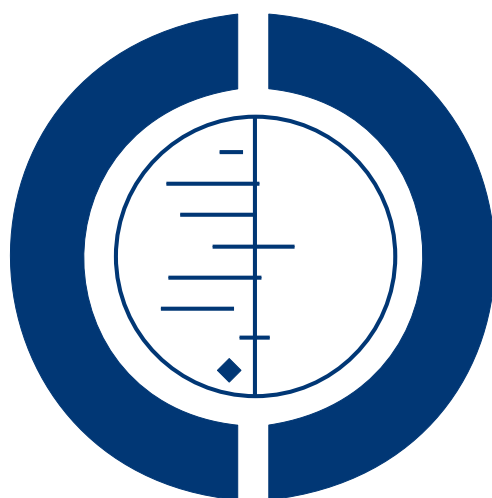


# Vitamin E supplementation for prevention of morbidity and mortality in preterm infants (Review)

Brion LP, Bell EF, Raghuveer TS



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Vitamin E supplementation for prevention of morbidity and mortality in preterm infants (Review)  
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[Intervention Review]

# Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

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**Editorial group:** Cochrane Neonatal Group.

**Publication status and date:** Edited (no change to conclusions), published in Issue 4, 2008.

**Review content assessed as up-to-date:** 30 March 2007.

**Citation:** Brion LP, Bell EF, Raghuvver TS. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD003665. DOI: 10.1002/14651858.CD003665.

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## ABSTRACT

### Background

Treating very low birth weight (VLBW) infants with pharmacologic doses of vitamin E as an antioxidant agent has been proposed for preventing or limiting retinopathy of prematurity, intracranial hemorrhage, hemolytic anemia, and chronic lung disease. However, excessive doses of vitamin E may result in concerning side effects.

### Objectives

To assess the effects of vitamin E supplementation on morbidity and mortality in preterm infants.

### Search strategy

MEDLINE (October 2002), EMBASE (March 2002), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2003), and personal files for clinical trials assessing vitamin E in preterm infants were searched. The MEDLINE and CCTR searches were updated in March 2007.

### Selection criteria

Trials analyzing primary outcomes (mortality or combined long-term morbidity) or secondary outcomes (other morbidity) in infants with gestational age less than 37 weeks or birth weight less than 2500 grams were selected. The intervention was allocation to routine supplementation with vitamin E in the treatment group versus placebo, no treatment or another type, dose or route of administration of vitamin E.

### Data collection and analysis

The standard methods of the Cochrane Collaboration and of the Cochrane Neonatal Review Group were used.

### Main results

Twenty-six randomized clinical trials fulfilled entry criteria. No study assessed combined long-term morbidity. Routine vitamin E supplementation significantly increased hemoglobin concentration by a small amount. Vitamin E significantly reduced the risk of germinal matrix/intraventricular hemorrhage and increased the risk of sepsis; however, heterogeneity limits the strength of these latter

two inferences. Vitamin E did not significantly affect other morbidity or mortality. In VLBW infants, vitamin E supplementation significantly increased the risk of sepsis, and reduced the risk of severe retinopathy and blindness among those examined.

Subgroup analyses demonstrated (1) an association between intravenous, high-dose vitamin E supplementation and increased risk of sepsis and of parenchymal cerebral hemorrhage; (2) an association between vitamin E supplementation by other than the intravenous route and reduced risk of germinal matrix-intraventricular hemorrhage and of severe intraventricular hemorrhage; and (3) an association between serum tocopherol levels greater than 3.5 mg/dl and increased risk of sepsis and reduced risk for severe retinopathy among those examined.

### Authors' conclusions

Vitamin E supplementation in preterm infants reduced the risk of intracranial hemorrhage but increased the risk of sepsis. In very low birth weight infants, vitamin E increased the risk of sepsis, and reduced the risk of severe retinopathy and blindness among those examined. Evidence does not support the routine use of vitamin E supplementation by intravenous route at high doses or aiming at serum tocopherol levels greater than 3.5 mg/dl.

## PLAIN LANGUAGE SUMMARY

### Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Giving extra vitamin E to preterm babies can provide some benefits, but it increases the risk of life-threatening infections. Preterm babies (born before 37 weeks) can develop a range of problems because their organs are not mature. Vitamin E may be able to help prevent or limit some of these problems, but it can potentially also have harmful effects. Breast milk of a woman who has given birth prematurely has higher than usual levels of vitamin E. Preterm babies can be given extra vitamin E as vitamin drops, in vitamin E-enriched formula, in intravenous fluids, or by injection into their muscles. This review of studies of vitamin E supplements found that while extra vitamin E reduces the chances of some complications (including disease of the retina), the risk of life-threatening infection is increased. The risk of bleeding in the brain is increased when extra vitamin E is given by vein but decreased when the extra vitamin E is given by other routes.

## BACKGROUND

### 1. What is vitamin E?

Vitamin E comprises a group of eight biologically active tocopherols, among which d-alpha-tocopherol has the highest antioxidant activity per mg of tocopherol (1.49 international unit [IU]/mg). The IU is defined as the biological activity of 1 mg of dl-alpha-tocopheryl acetate. One mg of d-alpha-tocopherol equivalent equals the activity of 1 mg of d-alpha-tocopherol. Vitamin E is one of several antioxidants that preterm infants can use as scavengers of free radicals, thereby potentially limiting processes which can lead to chronic lung disease and retinopathy of prematurity (Thibeault 2000) and other long-term complications (Brigelius-Flohé2002). In addition, alpha-tocopherol inhibits inflammation by modulating cellular signaling and by regulating transcription, and stimulates immunity; a metabolite of gamma-tocopherol has

been proposed as a natriuretic factor (Brigelius-Flohé2002) .

### 2. Do preterm infants need vitamin E, and what is their requirement of this vitamin?

The content of alpha-tocopherol in the body of the fetus remains at 3-7 mg/kg throughout gestation (Bell 1981). In preterm infants, lack of vitamin E intake or fat malabsorption results in edema, thrombocytosis and hemolytic anemia and could eventually result in spinocerebellar degeneration. Signs of this deficiency are enhanced by iron supplementation (due to its oxidant activity) and by high concentration in milk formula of linoleic acid and other polyunsaturated fatty acids (PUFA), which are subject to oxidation (Hassan 1966; Oski 1967; Ritchie 1968; Williams 1975). The clinical assessment of vitamin E deficiency remains a challenge in preterm infants, because serum tocopherol levels may not

reflect tissue levels and depend on serum lipid levels (Greer 2000). A tocopherol/total lipid ratio of greater than 0.8 mg/g has been recommended as an indication of vitamin E sufficiency (Johnson 1998).

The amount of vitamin E in colostrum and preterm milk is approximately two to three times that in mature milk (Gross 1993). Formulas for preterm infants should contain at least one IU of vitamin E per gram of linoleic acid, 0.6 mg of d-alpha-tocopherol equivalent per g of PUFA (Bell 1981) and 0.7 IU per 100 kcal in order to prevent vitamin E deficiency (Gross 1993; Committee N 1985). With these doses, hemolytic anemia of vitamin E deficiency has been virtually eliminated except in rare cases of prolonged total parenteral nutrition with lipid emulsion and inadequate supplemental vitamin E or in cases of fat malabsorption due to cholestatic liver disease or to cystic fibrosis (Bell 1987). The American Academy of Pediatrics Committee on Nutrition has recommended daily supplementation of 5-25 IU of vitamin E in preterm infants to ensure enough accretion (Committee N 1985); however, such supplementation might not be necessary (Gross 1985).

The optimal amount of parenteral vitamin E in preterm infants is uncertain, although the maximum recommended dose for any neonate is 7 IU per day (5 ml of M.V.I. Pediatric®, Astra Pharmaceuticals, L.P., Wayne, PA). The manufacturer's recommendation is 1.5 ml/day for infants weighing less than 1 kg, 3.25 ml/day for those weighing 1 to 3 kg, and 5 ml/day for infants and children weighing 3 kg or more and up to 11 years of age. The American Academy of Pediatrics has recommended a standard dose for all preterm infants: 40% of a vial of M.V.I. Pediatric® (Committee N 1998). Using a fixed dose per day (regardless of exact weight), serum alpha-tocopherol levels at one week of life are inversely related with birth weight (Amorde-Spalding 1992; Phillips 1987), and some infants develop serum levels greater than 3.5 mg/dl (Amorde-Spalding 1992; DeVito 1986; MacDonald 1987; Phillips 1987). The American Society for Clinical Nutrition recommends a parenteral dose of vitamin E of 2.8 IU/kg/day for preterm infants and 7 IU/day in full-term infants (Greene 1988). This dose is met by standard intravenous vitamin solutions (Gross 1993; Greer 2000): a dose of 2.8 IU/kg/day is provided by 1 ml of a vial of M.V.I. Pediatric® Solution for infants with a weight of 500 g and by 2 ml for a weight of 1000 g. Schwalbe has recommended a dose of d,l-alpha-tocopheryl acetate of 4.5 mg/kg/day (4.5 IU/kg/day) for very low birth weight infants based on serum levels during the first 2 weeks of life after a five-day infusion (Schwalbe 1992). In preterm infants with birth weight 820-2000 g, vitamin E at an average dose of 3 IU/kg/day administered intravenously by continuous infusion in multivitamins for 3-4 weeks generally yields plasma levels within the normal range (1-3 mg/dl) (Gutcher 1985; Baeckert 1988).

3. What is the rationale for vitamin E supplementation in preterm infants; what is the bioavailability; what is the potential indirect

and direct toxicity of vitamin E supplements; and is there a safe dose?

Supplementing very low birth weight infants with vitamin E as an antioxidant agent has been proposed for preventing or limiting retinopathy of prematurity, intracranial hemorrhage, and chronic lung disease. Nevertheless, tissue levels reached by pharmacologic doses of vitamin E are several fold higher than those required to produce maximum antioxidant effect (Roberts 1987).

At steady state, umbilical cord blood serum, plasma or erythrocyte levels of tocopherol are related to, but less than half maternal levels and increase progressively during pregnancy (Navarro 1984; Cachia 1995; Jain 1996; Johnson 1998; Chan 1999; Baydas 2002; Bolisetty 2002). One study has shown that the administration of 300-600 mg of vitamin E to the mother during preterm labor may reduce the risk of neonatal intracranial hemorrhage diagnosed at non traumatic spinal tap or autopsy (1/45 in the treated group versus 6/45 in controls, RR 0.17, CI 0.02,1.33; RD -0.11, CI -0.22) (Minkowski 1949). Nevertheless, two other studies have shown that fetal cord plasma levels of tocopherol fail to increase after three days of maternal supplementation (Léger 1998) and within nine days of maternal supplementation only increase up to values lower than half those required to reduce hemolysis (Cruz 1983). Approximately 30% of the mothers have levels consistent with vitamin E deficiency (Cachia 1995), and a daily maternal intake of 400 IU of vitamin E has been estimated to prevent or correct such deficiency (Woods 2001). In a cohort of 1231 gravid women, maternal plasma concentrations of alpha-tocopherol in early pregnancy and at 28 weeks were positively associated with fetal growth (Scholl 2006).

Most but not all studies support the observation that enteral absorption of vitamin E in preterm infants is sufficient to rapidly achieve adequate blood levels of tocopherol (Bell 1987). Neonatal serum tocopherol levels increase progressively when fed human colostrum, which is rich in vitamin E (Gross 1993; Moran 1983; Ostrea 1986), or formula, which now routinely contains vitamin E. In preterm infants, enteral absorption of vitamin E from water-soluble preparations is better than from lipid-soluble preparations (Gross 1974; Jansson 1984). Intramuscular absorption of alpha-tocopheryl acetate prepared in solution in olive oil, available in several European countries, is six times lower than that of vitamin E in colloidal solution, available in England and North America (Bonati 1991). When vitamin E is provided as alpha-tocopheryl acetate, bioavailability of free vitamin E (tocopherol) requires hydrolysis, which is mediated by an enzyme (esterase). This hydrolysis is a limiting step in case of parenteral administration (Newmark 1975; Pedraz 1989) but not in case of enteral administration (Bell 1979 [see Zipursky 1987]), because of abundance of pancreatic and jejunal mucosal esterase activity (Mathias 1981). These observations explain why even a small dose of 5 mg of dl-alpha-tocopheryl acetate provided enterally has proven to be more efficient than larger intramuscular doses (30 mg) in treating scleredema (



Gerl6czy 1949).

Vitamin E toxicity may be related to the dose, chemical form, route of administration, or (in the case of parenteral forms) speed of administration, or to some combination of these factors (Bell 1987; Hale 1995). Risks associated with vitamin E excess in adult humans (Bell 1989) include (1) impaired resistance to infection resulting from decreased leukocyte function, and (2) increased bleeding resulting from a decrease in vitamin-K-dependent factors in vitamin-K deficient individuals (Corrigan 1979) and inhibition of platelet prostaglandin synthesis and of platelet aggregation (Stuart 1979). Reports of toxicity of enteral vitamin E are rare in infants. Enteral intake of vitamin E up to 25 mg/kg/day rarely yields serum levels greater than 3.5 mg/dl (81 micromol/L), i.e., the levels associated with an increased incidence of sepsis and necrotizing enterocolitis (Bell 1989). The safe upper limit of vitamin E in infant formulas was estimated to be 10 mg d-alpha-tocopherol equivalent per 100 kcal or 15 IU/100 kcal, which would provide half the amount of enteral vitamin E (25 mg/kg/day) that appears to be safe and well tolerated (Bell 1989). This dose also corresponds to the highest concentration of vitamin E in colostrum (~60 mg/dl). Johnson has recently proposed to classify serum tocopherol levels as physiologic (1-3.5 mg/dl), proposed for prophylaxis and treatment of early retinopathy of prematurity, and pharmacologic (4-5 mg/dl), proposed for treating severe retinopathy of prematurity (Johnson 1995). Increased necrotizing enterocolitis has been observed in patients with serum concentration of vitamin E greater than 3.5 mg/dl while receiving a total (intravenous vitamins, intravenous lipid solution, formula and oral vitamin supplementation 0-25 mg/kg/day) vitamin E dose less than 25 mg/kg/day (Friedman 1988).

Fifty-eight infants at a single institution received pharmacologic doses (25-50 IU/kg/day intravenously) of a new preparation of vitamin E (E-Ferol®, O'Neal, Jones and Feldman, Maryland Heights, MO), which contained dl-alpha-tocopheryl acetate solubilized at 25 IU/ml with 9% polysorbate 80 and 1% polysorbate 20. Among these 58 infants, eight developed pulmonary deterioration, liver failure (hepatomegaly, ascites, and in some cases cholestatic jaundice and hypoproteinemia), thrombocytopenia, and renal failure, and five died (Lorch 1985). Review of autopsy-derived tissue from 20 infants showed vascular hepatotoxicity characterized by progressive intralobular cholestasis, inflammation of hepatic venules, and extensive sinusoidal veno-occlusion by fibrosis (Bove 1985). Two subsequent retrospective reports described E-Ferol®-related events (Martone 1986; Arrowsmith 1989). A total of 38 deaths were attributed to E-Ferol®, which was removed from the market. It remains unclear whether the toxicity of E-Ferol® resulted from the vitamin E itself, its preparation as tocopheryl acetate (which could not be hydrolyzed when given intravenously), the polysorbates present in the product, or an undetermined contaminant (Balistreri 1986; Bell 1987). Parenteral vitamin E administration (either dl-alpha-tocopheryl acetate, or free dl-alpha

tocopherol in ethanol) caused dose-related toxicity in kittens, including hepatosplenomegaly and mortality (Phelps 1987b). Toxicologic studies (see Arrowsmith 1989; Balistreri 1986; Alade 1986) suggested that the effects of E-Ferol® could be at least in part reproduced by high doses of polysorbates 20 and 80. However tissue accumulation of vitamin E and tissue changes after E-Ferol® administration depended on the dose, route and duration of administration, with toxicity associated with rapid intravenous administration (Hale 1995).

A retrospective analysis has shown a significant association between pharmacologic oral doses of vitamin E (diluted 1:2, provided at a dose of 200 mg/day in eight aliquots) in very low birth weight infants and necrotizing enterocolitis (Finer 1984). Necrotizing enterocolitis was attributed to the high osmolality of the undiluted solution, 4050 mOsm/kg, in turn related to its high content of propylene glycol (daily dose of 200 mg tocopherol, 800 mg propylene glycol, 800 mg sorbitol, 1 g polysorbate 80 in 4 ml water). Alternatively, toxicity may have been related to direct toxicity of vitamin E or of propylene glycol. The dose of propylene glycol was almost three times as much as a well-tolerated daily dose (300 mg propylene glycol and 1 mg vitamin E in 1 ml M.V.I.-Concentrate®, Armour Pharmaceutical Co, Kankakee, IL) resulting in serum propylene glycol levels greater than 40 mg/dl in 14/30 very low birth weight infants (MacDonald 1987). The incidence of necrotizing enterocolitis decreased when this formulation was later replaced with an isotonic solution without propylene glycol.

Soft tissue calcification has been reported in two patients after intramuscular administration of vitamin E (Barak 1986).

4. Why are systematic reviews of vitamin supplementation in preterm infants and subgroup analyses needed?

Existing reviews (Ehrenkranz 1980; Bell 1981; Bell 1987; Phelps 1985; Phelps 1987; Phelps 1988; Bell 1989; Law 1990; Muller 1992; Gross 1993; Baley 1992; Bell 1992; Doyle 1992; Ehrenkranz 1992; Watts 1992; Raju 1997; Greer 2000) have assessed only some of the effects of vitamin E on mortality and morbidity in preterm infants or very low birth weight infants. The present systematic review analyzes a broader spectrum of risks and benefits of vitamin E supplementation, in preterm infants and in very low birth weight infants. Subgroup analyses are required to determine which factors affected the responses to vitamin E supplementation.

Subgroup analyses were designed to determine if the effects of vitamin E supplementation on morbidity and mortality in preterm infants depend on:

(1) Gestational age: The most immature infants body content of vitamin E at birth is lower and the risks for many of the outcome variables are higher. Birth weight could be used if gestational age is not available

(2) Vitamin E preparation and route of administration: This may affect vitamin E absorption, distribution and toxicity. The latter may result (1) from direct tissue toxicity of vitamin E and/or (2) from specific reagents, e.g., polysorbates 80 and 20 ([Arrowsmith 1989](#); [Lorch 1985](#)), or propylene glycol, which can unduly increase osmolality, thereby increasing the risk of necrotizing enterocolitis ([Finer 1984](#)).

(3) The total daily dose of vitamin E, i.e., the sum of supplemented vitamin E and the dose contained in the formula and in parenteral nutrition in both groups, and serum tocopherol levels.

(4) Time of initiation of vitamin E supplementation: This is especially important for outcome variables which appear early (e.g., intraventricular hemorrhage) and those in which early onset of free radical-related damage and inflammation is expected (e.g., chronic lung disease)

(5) Intake of other nutritional components, which may modify the risk of production of free radicals and serum tocopherol levels ([Gross 1985](#)). These may include oxidants (e.g., iron), antioxidants (e.g., selenium, vitamin A) and oxidizable nutrients (e.g., PUFA).

(6) Selection bias: randomized trials (which prevent selection bias) only versus all controlled studies. To limit the size of this review, this subgroup analysis was eliminated (see below).

## OBJECTIVES

To assess the effects of vitamin E supplementation on morbidity and mortality in preterm infants. Secondary aims included subgroup analyses designed to determine if the effect of vitamin E supplementation depends on the factors delineated above (see Background, last paragraph).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized or quasi-randomized controlled clinical trials in which at least one of the primary or secondary outcome variables (see below) has been analyzed. After obtaining all possibly eligible trials, it became evident that many large, well-designed randomized trials were available. We therefore decided to eliminate all nine quasi-randomized trials from the analyses.

#### Types of participants

Preterm infants (gestational age less than 37 weeks). Trials were included regardless of the vitamin E intakes of the infants' mothers during pregnancy.

After obtaining all possibly eligible trials, it became evident that many trials assessing the effect of vitamin E on important outcome variables in neonates had used birth weight rather than gestational age. Therefore, eligibility criterion were modified to either gestational age less than 37 weeks or birth weight less than 2500 grams.

#### Types of interventions

Randomized or quasi-randomized allocation of the infant to routine supplementation with vitamin E in the treatment group versus either placebo, no treatment or another type, dose or route of administration of vitamin E. Studies were accepted regardless of the vitamin E content of the infant's feedings (human milk or formula). The treatment group may have received vitamin E supplement either enterally or parenterally, and at any dose. However, studies assessing the effect of another intervention, to which vitamin E was only a co-intervention (e.g., studies assessing the effect of erythropoietin on hemoglobin concentration, in which vitamin E and iron were provided only in the treatment group) were excluded.

#### Types of outcome measures

Primary outcome measures included mortality, combined outcome at 18 months including mortality [mortality, bronchopulmonary dysplasia, blindness, mental retardation or cerebral palsy], and combined outcome at 18 months excluding mortality [bronchopulmonary dysplasia, blindness, mental retardation or cerebral palsy].

Secondary outcome measures include the following:

E-Ferol-related "clinical syndrome" as defined earlier ([Arrowsmith 1989](#)), combined outcome (either mortality before discharge, bronchopulmonary dysplasia, severe retinopathy of prematurity, severe cerebral abnormality, blindness, mental retardation, or cerebral palsy), bronchopulmonary dysplasia (current definition: continuous positive airway pressure or oxygen requirement at 36 weeks corrected age), patent ductus arteriosus, sepsis, severe intraventricular hemorrhage (Papile grade III or IV), mild-to-moderate intracranial hemorrhage (Papile stage I or II), severe cerebral abnormality [either intraventricular hemorrhage grade III or IV, cystic periventricular leukomalacia or severe ventricular dilatation], severe retinopathy of prematurity (grade 3 or worse), retinopathy of prematurity, necrotizing enterocolitis with gastrointestinal perforation, necrotizing enterocolitis not requiring surgery, renal failure (serum creatinine concentration above 1.5 mg/dl), signs of hemolysis (anemia, reticulocyte count, hemoglobin concentration, need for transfusion, number of transfusions, bilirubin concentration), platelet count, coagulation tests, and local reaction at the injection

site. Studies which reported only serum or plasma tocopherol levels but none of the above mentioned clinical outcomes were not included.

## Search methods for identification of studies

See Collaborative Review Group Strategy.

MEDLINE accessed using PubMed in October 2002 (1966 - 2002), EMBASE in March 2002 (1974 - 2002), and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2003 and Issue 1, 2007). We examined reports in any language as long as the report included an abstract in English. The MEDLINE search was repeated in April 2003 and March 2007.

The MEDLINE search was done using the following search terms: (<vitamin E> OR <tocopherol>). The search was limited to <birth -23 months> AND (<randomized clinical trial> OR <controlled clinical trial>). Because this search yielded many studies conducted in children, it was re-done using (<vitamin E> OR <tocopherol>) AND (prematurity OR preterm).

The EMBASE search was done using the following search terms: (Exp alpha tocopherol OR vitamin E.mp. OR \*tocopherol/) AND (exp prematurity/OR preterm.mp.). The search was limited to (human and infant < to one year>).

Selection was done independently by three investigators; any disagreement was resolved by discussion.

The CCTR does not accept searches using single-letter words. Therefore the search was done using the following search terms: Tocopherol AND (prematurity OR preterm) AND infant.

Personal files were searched and reviewed relevant references cited in the other manuscripts.

## Data collection and analysis

The standard methods of the Cochrane Neonatal Review Group (CNRG) were used.

<http://neonatal.cochrane.org/>

*“Organization and Methodology of a Systematic Review for CNRG (Guidelines for Reviewers & Editors)”*

These included independent review of all candidate studies by all reviewers. The methodological quality of the trials was assessed by analyzing the risk of four types of bias: selection, performance, attrition and detection.

Standard methods of the CNRG were used for estimating treatment effects with 95% confidence interval (CI) and a fixed effect model. Dichotomous variables were assessed using relative risk (RR), risk difference (RD), and number needed to treat/harm. Data were extracted on as many randomized patients as possible, and analyzed on an intent-to-treat basis, using as denominator for dichotomous variables the total number of randomized patients. Since several studies have reported specific outcome variables only

in selected subgroups subject to attrition bias (e.g., survivors) the names of the variables were modified accordingly. Exceptionally, the total number of patients in each arm of the study was not available because the authors have excluded patients from the study after randomization; in this case, the maximum number of available patients was used instead of the total number of randomized patients. Data reported in very low birth weight infants were treated as separate variable, to allow subgroup analyses in this important population. Continuous variables are presented as mean  $\pm$  1 standard deviation (SD). Where justified clinically, we merged two or more subgroups of a published study, using standard formulae to calculate the weighted mean and to estimate the weighted standard deviation (Altman 1991; Brion 1990; Zahr 1984). Continuous variables were assessed by the weighted mean difference (WMD) between the treatment group and the control group.

Additional data including those obtained after or pending publication were requested from the authors, if necessary.

### I. Original plan:

To analyze studies separately according to the amount of vitamin E provided to the mother during pregnancy, and according to the amount, type or route of vitamin E supplementation of the infants in the control group:

1. Analysis excluding studies with documented prolonged (>1 week) high-dose ( $\geq$  400 mg/day) vitamin E supplementation during pregnancy

1.1 Infant provided with placebo, with total daily dose of vitamin E < 10 mg/100 kcal

1.2. Infant provided with another dose of vitamin E (total intake >10 mg/100 kcal)

1.3. Infant provided with another type or route of vitamin E formulation

2. Analysis of studies with documented prolonged (> 1 week) high-dose ( $\geq$ 400 mg/day) vitamin E supplementation during pregnancy

2.1. Infant provided with placebo, with total daily dose of vitamin E < 10 mg/100 kcal

2.2. Infant provided with another dose of vitamin E (total intake >10 mg/100 kcal)

2.3. Infant provided with another type or route of vitamin E formulation

Subgroup analyses planned:

1. Gestational age:

1.1.  $\geq$  29 weeks

1.2. < 29 weeks

If gestational age is not available or is not the cut-off for the trials:

1.3. Birth weight > 1000 g

1.4. Birth weight  $\leq$  1000 g

2. Medication given in the treatment group:

2.1. Route of administration and formulation:

2.1.1. Enteral

2.1.1.1. Enteral lipid form - isotonic to mildly hypertonic (< 400 mOsm/kg)

- 2.1.1.2. Enteral lipid form - hypertonic ( $\geq 400$  mOsm/kg)
- 2.1.1.3. Enteral aqueous form
- 2.1.2. Parenteral
  - 2.1.2.1. Parenteral, excluding polysorbate
  - 2.1.2.2. Parenteral colloidal, excluding polysorbate
  - 2.1.2.3. Parenteral colloidal with polysorbate
  - 2.1.2.4. Parenteral olive oil
- 3. Total dose of vitamin E provided (iv + diet + supplement)
  - 3.2.1.  $<25$  mg/kg/day
  - 3.2.2.  $\geq 25$  mg/kg/day
- 4. Time of onset of vitamin E supplementation in the treatment group
  - 4.1. Within the first 48 hours of life
  - 4.2. After the first 48 hours of life
  - 4.3. After 4 weeks of life
- 5. Other nutritional components which may modify the effects of or the need for vitamin E
  - 5.1 Iron supplementation
    - 5.1.1. Iron supplementation  $> 2$  mg/kg/day in both groups
    - 5.1.2. Iron supplementation  $> 2$  mg/kg/day in treatment group only
    - 5.1.3. Iron supplementation  $\leq 2$  mg/kg/day
  - 5.2. PUFAs
    - 5.2.1. Formula with PUFAs  $>400$  mg/100 ml formula in both groups
    - 5.2.2. Formula with PUFAs  $<400$  mg/100 ml formula in both groups
    - 5.2.3. Formula with PUFAs  $>400$  mg/100 ml formula in treatment group
  - 5.3. Dietary or parenteral supplementation with one or more other antioxidants (in both groups)
    - 5.3.1. Selenium fortification  $\geq 3$  mcg/kg/day
    - 5.3.2. Vitamin A supplementation ( $\geq 1500$  U/day)
    - 5.3.3. Selenium fortification  $\geq 2$  mg/100 ml formula and vitamin A supplementation ( $\geq 1500$  U/day)
    - 5.3.4. Neither
- 6. According to study design:
  - 6.1. Randomized studies only
  - 6.2. All studies

## II. Modifications to the original plan:

Studies of vitamin E administration to preterm infants have been conducted for more than fifty years, during which standard of care including baseline vitamin E intake in pregnancy and in very low birth weight infants has changed considerably. Furthermore, the definitions of chronic lung disease of prematurity or bronchopulmonary dysplasia and of retinopathy or prematurity or retrolental fibroplasia have changed several times during the last decades. Several methods have been used to administer vitamin E, and some of the differences in design among studies became clear only during completion of the protocol.

Outcome variables in the available trials were often reported only in specific subgroups, e.g., very low birth weight infants. Because

very low birth weight infants are the only ones at risk for some of the complications potentially treated or prevented by vitamin E (e.g., severe retinopathy of prematurity), separate outcome variables were created in that weight group to allow subgroup analyses. This was the only way to determine which (or whether any) specific method of vitamin E administration (dose, duration, level, etc) is both efficient and nontoxic in very low birth weight infants. Subgroups among very low birth weight infants are referred to as "all studies" when they included all studies irrespective of the weight cut-off (either 1500 grams or 1000 grams), "equal to or less than 1500 grams" or "equal to or less than 1000 grams", as appropriate for each specific weight cut-off. For many outcome variables the first subgroup includes "all infants in all studies." An additional outcome variable that had not been anticipated was added as a post-hoc analysis: retinal hemorrhage.

In order to limit the number of comparisons, the main planned comparisons (listed in above sections 1 and 2) were replaced by the following:

1. Vitamin E versus placebo
  2. Vitamin E versus another form or route of vitamin E (intramuscular versus enteral, intravenous versus intramuscular, intramuscular in olive oil versus intramuscular in colloidal form)
- Many trials used combination of enteral and parenteral vitamin E supplementation, so these entries were modified as follows:

### 2. Route of administration and formulation:

- 2.1. Enteral
  - 2.1.1. Enteral hypertonic formulation at pharmacologic dose
- 2.2. Parenteral with or without enteral
  - 2.2.1. Parenteral with hypertonic enteral formulation at pharmacologic dose
  - 2.2.2. Parenteral colloidal with polysorbate
  - 2.2.3. Intravenous (with or without other routes of administration)
  - 2.2.4. Excluding intravenous administration

The cut-off value for vitamin E intake were clarified as follows:

3. Total daily dose of vitamin E provided (iv + diet + supplement) to the treatment group, target serum level
  - 3.1.  $\leq 20$  mg d-alpha-tocopherol equivalents/kg/d OR 30 IU/kg/d, i.e., 30 mg/kg/d dl-alpha-tocopheryl acetate\*
  - 3.2.  $> 20$  mg d-a-tocopherol equivalents/kg/d OR 30 IU/kg/d, i.e., 30 mg/kg/d dl-alpha-tocopheryl acetate\*

\* If the dose is expressed in IU/day or mg/day, we used mean birth weight (estimated, if necessary, to be 1000 g for studies on infants with birth weight  $< 1500$  grams) in the group for the calculations. Based on [Johnson 1995](#) an entry based on serum tocopherol levels at the end of the period of vitamin supplementation was added:

- 3.3. Serum tocopherol level  $\leq 3.5$  mg/dl (81 micromoles/L)
- 3.4. Serum tocopherol level  $> 3.5$  mg/dl

Subgroup analyses were added based on duration of the treatment:

4. Time of onset and duration of vitamin E supplementation in the treatment group
  - 4.1. Within the first 48 hours of life

- 4.2. After the first 48 hours of life
  - 4.3. Duration of treatment  $\leq$  1 week (7 daily doses)
  - 4.4. Duration of treatment  $>$  1 week (7 daily doses)
- Since only randomized trials were included for this review, the subgroup analysis of randomized trials was eliminated. Vitamin E administration during pregnancy and dose of vitamin E in the control group is addressed as subgroup analyses instead of main comparisons:
6. Vitamin E provided during pregnancy
    - 6.1. Documented prolonged high-dose (at least 400 IU/day for a week) vitamin E during pregnancy
  7. Total dose of vitamin E provided to the control group
    - 7.1.  $\leq$  10 mg vitamin E/100 kcal
    - 7.2.  $>$  10 mg vitamin E/100 kcal

Subgroup analyses based on other nutritional components that may modify the effects of or the need for vitamin E were assessed as planned, except comparisons in which vitamin E was a co-intervention with one of those supplements were eliminated. Because these studies have spanned more than 50 years of research, definitions of outcome variables such as retrolental fibroplasia (retinopathy of prematurity) and bronchopulmonary dysplasia have changed. Only entries for which we found relevant studies are presented in the Table of Comparisons.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

The MEDLINE search retrieved 128 studies, the EMBASE search 35 studies and the CCTR search 14 studies. Review of personal files and reading of documents obtained by the initial searches and by screening all references listed in manuscripts yielded more than 50 additional studies. An updated search of the MEDLINE and the CCTR conducted in March 2007 yielded one additional retrospective study ([Liu 2005](#)). After excluding ineligible studies and after merging multiple publications of the same studies, a total of 62 trials remained. Twenty-six randomized clinical trials (range of patients per trial: 10-914) were included in this systematic review. Among these 26 trials, five were conducted in the 1970's, 17 in the 80's, three in the 90's and one in 2003.

Only those trials that prospectively compared a group of vitamin E-supplemented neonates with a control group are reported in the Tables of Included and Excluded Studies. Thirty-five studies are listed in the Table of Excluded Studies. Studies were placed in this group for the following reasons (some studies for more than one reason): (1) trials (n=18) that did not assess any of the predefined outcomes or did not provide analyzable outcomes because

either mean and variability (standard error of the mean or standard deviation), frequencies or individual data were not available, (2) studies (n=7) in which the experimental group and the control group were not enrolled simultaneously, (3) quasi-randomized trials (n=12, of which three had at least one additional criterion of exclusion), defined as trials in which patients were not randomly allocated to the treatment and the control arms of the study, (4) trials (n=3, two of which also fitted the first criterion) in which either no preterm infants had been enrolled or a mixture of full-term and preterm infants had been enrolled and (5) trials (n=1) in which vitamin E was only a co-intervention. A complete list of 51 additional publications (case series, reviews, retrospective chart reviews) that were considered but are not reported in this systematic review is available upon request.

Although the classical definition of very low birth infants is a birth weight less than 1500 grams, studies assessing the effect of vitamin E on outcomes in preterm infants used a birth weight equal to or less than 1500 grams. In order to shorten the text, the term "very low birth weight infants" is used to refer to this latter group.

#### 1. Vitamin E versus placebo

This group included 25 randomized trials that assessed the effects of vitamin E supplementation by enteral route only (n=8), intramuscular with or without enteral (n=15), or intravenous with or without other routes (n=2). Vitamin E supplementation was initiated within the first 48 hours of life in all treated patients in 20 studies, and after 48 hours in all treated patients in four studies. The duration of vitamin E supplementation was up to one week in eleven studies and greater than one week in all patients in thirteen studies. The total dose of vitamin E intake in the treated group was equal to or less than 30 IU/kg/day in fifteen studies and greater than 30 IU/kg/day in nine studies. Serum tocopherol levels were up to 3.5 mg/dl in fifteen studies and greater than 3.5 mg/dl in eight studies. The total dose of vitamin E intake in the control group was up to 10 mg/100 kcal in 22 studies and greater than 10 mg/100 kcal in three studies.

[Chiswick 1982](#) is a randomized trial assessing the effect of four daily intramuscular injections of 20 mg/kg/dose of dl-alpha-tocopherol acetate as an aqueous colloidal solution (Ephynal®, Hoffmann-La Roche, Basel, Switzerland) starting at 24 hours of age on mortality and intraventricular hemorrhage in preterm infants. Entry criteria were: preterm infants without major congenital malformations. The concentration of the solution was 1000 mg/2 ml, and individual doses greater than 0.5 ml were divided and given in two different injection sites. Controls received no injection of vitamin E. Only five infants, i.e., those without respiratory distress, received formula (SMA Gold Cap Milk®, Wyeth Laboratories, Slough, England) during the first four days of life. The total number of patients entered into the study was 35, including 14 in the treatment group and 21 in the control group. Gestational ages ranged from 25 to 36 weeks (average  $29.1 \pm 3.3$  weeks in the treated group and  $29.3 \pm 3.3$  weeks in the control group) and birth weights from 550 to 1750 g (average  $1.21 \pm 0.29$  kg in the treated



group and  $1.25 \pm 0.33$  kg in the control group). Intraventricular hemorrhage was diagnosed by computerized tomography, clinical findings (uniformly blood-stained cerebrospinal fluid, seizures, tense anterior fontanel) or autopsy. Because not all infants had a computerized tomography (number not provided) or an autopsy ( $n = 1$ ), it is possible that some cases of intraventricular hemorrhage may not have been diagnosed; for the calculations we only used demonstrated cases of intraventricular hemorrhage (in contrast with the authors who assumed that one patient had a hemorrhage). Outcome variables included mortality and intraventricular hemorrhage.

**Chiswick 1983** is a randomized trial assessing the effect of three intramuscular injections of 20 mg/kg/dose of dl-alpha-tocopheryl acetate as an aqueous colloidal solution (Ephynal®, Hoffmann-La Roche, Basel, Switzerland) given at 12, 36 and 60 hours of age on intraventricular hemorrhage in preterm infants. Entry criteria were gestational age less than 37 weeks and birth weight less than 1751 g. Controls received no injection of vitamin E. No information is provided about enteral intake of vitamin E. Intraventricular hemorrhage was diagnosed by ultrasonogram performed within the first 48 hours of life and at least once after 72 hours; repeat examinations were done where possible daily during the first week and less often afterwards. The total number of patients was 44, including 21 in the treatment group and 23 in the control group. Mean gestational ages and birth weights in the whole study population are not provided. Outcome variables included mortality, germinal matrix/intraventricular hemorrhage, and intraventricular hemorrhage.

**Cruz 1983** is a randomized controlled trial assessing the effect of four intramuscular injections of 25 mg/kg of vitamin E (on days one, two, four and eight, respectively) on hematologic parameters in preterm infants. Entry criteria were: (1) mothers admitted with threatened premature delivery at 26-34 weeks of gestation, (2) infants born to mothers admitted for threatened preterm delivery at 26-34 weeks of gestation and delivered with a weight less than 2300 g. All mothers of infants in the randomized trial received 900 mg of vitamin E (Ephynal®, Roche) daily for three days, followed by 100 mg daily until delivery. A non-randomized third group of infants, born to non-supplemented mothers, received no intramuscular vitamin E supplementation. All infants were fed banked breast milk, followed by an infant formula (Allomin). All infants received oral multivitamin drops starting on day five of life; this provided two mg of vitamin E daily. Among 55 infants enrolled in this trial, 27 were randomized to the experimental group and 28 to the control group. Mean gestational ages were  $32.8 \pm 1.9$  weeks and  $32.4 \pm 1.9$  weeks, respectively, in the experimental and in the control group, and mean birth weights were, respectively,  $1808 \pm 361$  and  $1817 \pm 357$  g. Outcome variables included retrolental fibroplasia, and bronchopulmonary dysplasia.

**Ehrenkranz 1982** is a double-blind randomized trial assessing the effect of repeated intramuscular injections of 20 mg/kg of Vitamin E Injectable® (Hoffmann-LaRoche) on neonatal outcomes. Entry

criteria included respiratory distress syndrome and informed consent. Injections were given upon admission to the study and 24, 48, and 168 hours later. Additional doses were given twice weekly as long as infants received oxygen therapy and could not tolerate feedings and vitamin supplements. Patients in the control group received same volumes of placebo, i.e., the vehicle. All infants initially received an intravenous protein solution containing vitamin E 2.5 U/L. Enteral feedings provided 16 U/L (formula) or 3 U/L (human milk). Patients tolerating feeds regularly were given oral vitamin E supplementation (Aquasol E®, USV Pharmaceutical Corp.) at a dose of 50 IU/day if weight was less than 1000 g and 25 IU/day if weight was greater than 1000 g. Among 100 patients enrolled into the study, 47 were in the experimental group and 53 in the control group. Average gestational ages were  $30.3 \pm 2.7$  and  $30.5 \pm 2.9$  weeks, respectively, in the experimental group and in the control group, and average birth weights were, respectively,  $1427 \pm 432$  and  $1425 \pm 466$  g. Outcome variables included mortality (NY Acad Sciences 1982, table I, page 454; with one additional later death in the treated group and three in the control group [page 458]), bronchopulmonary dysplasia (diagnosis based on clinical, radiologic and/or pathologic evidence), patent ductus arteriosus, patent ductus arteriosus requiring therapy, intraventricular hemorrhage, and retrolental fibroplasia (numerator: Table 5A (revised), Ehrenkranz, Ophthalmol 1982; 89: page 988; denominator: Ehrenkranz, Ann NY Acad Sci 1982, table I, page 454; data for very low birth weight: Hittner, NEJM 1982 page 868, Figure 1). A stage II retrolental fibroplasia in this study corresponds to a stage III from the current classification (NEJM 1982).

**Ferlin 1998** is a randomized trial assessing the effect of oral supplementation with 25 IU/day of vitamin E and 4 mg/kg/day of elemental iron (provided as iron sulfate) on hematologic parameters in preterm infants. Entry criteria included: birth weight less than or equal to 1600 g and gestational age less than or equal to 35 weeks, informed consent, stable clinical course, no blood transfusion, regular follow-up visits after discharge, and absence of interfering events that would require discontinuation of medications. Patients were randomly allocated into one of four groups: group I: placebo started on the fifteenth day of life, iron starting at two months of age; group II: 4 mg/kg/day iron started on the fifteenth day of life; group III: 4 mg/kg/day iron and 25 IU/day alpha-tocopherol (Roche) orally started on the fifteenth day of life; group IV: 25 IU/day vitamin E started on the fifteenth day of life. All infants received 1.5 IU vitamin E/day and 0.1 mg iron (in multivitamin preparation) starting on the seventh day of life. Iron supplementation was started at 2 months of age in patients who had not been supplemented with iron yet. The 40 patients enrolled in the study were distributed equally among the four groups. Median birth weights and quartiles were 1395 g (1210, 1510), 1315 g (1210, 1430), 1310 g (1290, 1420) and 1385 g (1260, 1540), respectively, in groups I through IV. For this systematic review we compared group III (treatment) with group II (control) and group IV (treatment) with group I (control). The only analyzable out-

come variable is hemoglobin concentration at two months of age; for this purpose, the individual data from Figure 2 was used.

**Finer 1982** is a randomized trial assessing the effect of serial intramuscular injections of vitamin E on neonatal outcomes in preterm infants. Entry criteria included: birth weight between 750 and 1500 g, appropriate for gestational age, and informed consent. Infants in the treated group received 25 mg vitamin E, two doses, administered intramuscularly respectively within 12 hours of birth and 12 hours afterwards; then 20 mg intramuscularly daily for 14 days, then 20 mg intramuscularly every three days for five doses; then either 100 U daily orally or (if feeds not tolerated) 20 mg intramuscularly every three days. Infants in the control group did not receive any injections. The osmolality of the oral preparation, used as a 1:1 dilution, was 2,025 mOsm/kg. Among 126 infants entered into the trial, 62 were allocated to the treatment group and 64 to the control group. Average birth weights and ranges were 1197 g (820-1460) in the treatment group and 1207 g (760-1500) in the control group, and average gestational ages were, respectively, 29.3 weeks (26-34) and 29.3 weeks (26-35). Outcome variables included bronchopulmonary dysplasia, patent ductus arteriosus, and necrotizing enterocolitis. Outcomes described in some Infants only include: acute or cicatricial stage of retrolental fibroplasia [Lancet 1982, Table V, page 1089] (patients surviving at least one month) and blindness from retrolental fibroplasia (patients examined).

**Fischer 1987** is a double-blind randomized trial assessing the effect of oral administration of d-alpha-tocopherol polyethylene glycol-1000-succinate, 50 mg/day for three doses on bilirubin and hemoglobin in preterm infants. However, several infants received only 25 mg/day. Entry criteria included birth weight less than 1,500 g, normal size for gestational age, and informed consent. Control infants received placebo. The total number of patients entered into the study was 28, including seventeen in the treatment group and 11 in the control group. Average birth weights were 1220±170 g in the treatment group and 1250±150 g in the control group, and average gestational ages were, respectively, 30±1 weeks and 32±2 weeks. Outcome variables included hemoglobin and bilirubin concentrations.

**Fish 1990** is a double-blind randomized trial assessing the effect of dl-alpha-tocopherol (Ephynal®, Hoffmann-La Roche) intramuscularly on neonatal outcomes in preterm infants. Entry criteria included birth weight equal to or less than 1000 g, postnatal age equal to or less than 24 hours, and informed consent. Exclusion criteria were: extremely poor condition upon admission or major congenital abnormalities. Vitamin E was provided in four intramuscular doses at 15, 10, 10 and 10 mg/kg on days one, two, four and six of life, respectively, in preterm infants. Doses of dl-alpha-tocopherol 10 mg/kg were administered intramuscularly every three days if the attending neonatologist felt that the infant could not tolerate oral vitamin E after 7 days of life. Control patients received a placebo. All neonates received oral dl-alpha-tocopheryl acetate (Aquasol E) 100 mg/kg/day beginning at ad-

mission; the dose was adjusted after day 7 to maintain total serum tocopherol level 0.5-3.5 mg/dl. The total number of patients entered into the study was 149, of which two were excluded after entry, 73 were in the treatment group and 74 in the control group. Average birth weights in the treatment group and in the control group were, respectively, 782±70 g and 783±76 g, and average gestational ages were, respectively, 26±1 weeks and 26±1 weeks. Outcome variables included mortality, intracranial hemorrhage, necrotizing enterocolitis, sepsis, patent ductus arteriosus, and local reaction at injection site.

**Graeber 1977** is a randomized trial assessing the effect of vitamin E supplementation (2 doses tested) and that of iron supplementation on neonatal outcomes in preterm infants. Entry criteria included birth weight less than 1500 g and gestational age less than 34 weeks. Exclusion criteria included ABO or Rh isoimmunization, hemoglobin value less than 13 g/dl at seven days of age, transfusion of whole blood or plasma at any age, transfusion of red blood cells after one week of age. Patients were divided into six groups according to the amount of vitamin E (none, 100, 125 or 150 mg/kg intramuscularly) and the amount of iron-dextran complex (none or 25 mg intramuscularly on days 7, 14, 21 and 28). Each vitamin E dose was divided into four doses on days one and two, and days seven and eight, respectively. For this systematic review we regrouped patients according to vitamin E allocation. Among 35 infants entered into the study twenty were randomized to vitamin E supplementation (treatment) and fifteen to no supplementation (control). Birth weight ranged from 940 to 1470 g (mean 1270 g). Outcomes included bronchopulmonary dysplasia and retrolental fibroplasia.

**Gross 1977** is a randomized trial assessing the effect of intramuscular administration of a total dose of 125 mg/kg tocopheryl acetate (Roche) on hemoglobin concentration in preterm infants. Entry criteria included birth weight less than 2,500 g, gestational age less than 36 weeks, well, breathing room air, and hemoglobin concentration greater than 13 g/dl on the third day of life. Exclusion criterion was either Rh or ABO isoimmunization. Vitamin E was given in eight divided doses, an injection in each thigh, on days four, five, six and seven of life. Controls received no injection. Neither group received iron supplementation. The twenty patients entered into the study were equally divided into the treatment group and the control group. Mean gestational ages in the treatment group and in the control group were, respectively, 33.5±1.7 and 33.2±1.4 weeks, and mean birth weights were, respectively, 1717±176 and 1631±397 g. The outcome variable was hemoglobin concentration.

**Gross 1979** is a randomized controlled trial assessing the effect of intramuscular administration of a total dose of 50 mg/kg dl-alpha-tocopheryl acetate (Roche) administered intramuscularly in 6 divided doses, an injection in each thigh on days one, two and three of life. Entry criteria were birth weight between 1000 and 2000 g, and appropriate for gestational age. Exclusion criteria included hemoglobin concentration less than 13 g/dl, and Rh or

ABO isoimmunization. Infants in the control group received no injection. Neither group received iron supplementation. Among the 40 patients entered into the study, twenty were assigned to the treatment group and twenty to the control group. Eligible infants had a birth weight between 1000 and 2000 g and were appropriate for gestational age; average weight values are not provided. The outcome variable we used for this review was serum bilirubin concentration on day four of life.

**Hittner 1981** is a randomized trial assessing the effects of enteral administration of 100 mg/kg/day of dl-alpha-tocopheryl acetate (Aquasol E®, preparation containing Tween 80, propylene glycol, sorbitol, oil of anise, sodium saccharin, imitation butterscotch flavor) from the first day of life until discharge. Entry criteria included birth weight less than or equal to 1500 g, requiring oxygen for respiratory distress, admitted to the unit within the first 24 hours of life, and informed consent. Exclusion criteria included necrotizing enterocolitis preventing oral administration of vitamin E ( $n = 1$ ). Patients who died within four weeks ( $n = 48$ ) were excluded from all other outcomes. Osmolality of the enteral vitamin E preparation was 3000 mOsm/L (**Hittner 1984**). Control infants received a placebo solution. The total number of patients entered into the study was 150, including 75 allocated to the treatment group and 74 to the control group. Mean gestational ages in the treatment group and in the control group were, respectively,  $29.3 \pm 2.2$  and  $29.4 \pm 2.0$  weeks, and mean birth weights  $1093 \pm 245$  and  $1113 \pm 245$  g. Outcome variables included (1) mortality (data from NEJM 1981, Figure 1, page 1367), and (2) among patients surviving at least four weeks and without necrotizing enterocolitis: bronchopulmonary dysplasia, patent ductus arteriosus, sepsis, periventricular-intraventricular hemorrhage and retrolental fibroplasia.

**Hittner 1984** is a randomized trial assessing the effect of intramuscular administration of dl-alpha-tocopherol, 55 mg/ml (Ephynal®, Hoffman-La Roche, preparation containing benzyl alcohol, propylene glycol, ethyl alcohol, Emulphor E1-620, and buffering salts) at doses of 15, 10, 10, and 10 mg/kg on days 1, 2, 4 and 6 of life, respectively, in preterm infants. Entry criteria included birth weight equal to or less than 1,500 g, oxygen requirement for respiratory distress, admission within 24 hours, and informed consent. Patients who died before 10 weeks of life ( $n = 33$ ) were excluded from all other outcomes. Controls received placebo injections. Vitamin E 100 mg/kg/day was given orally to all infants starting within the first 24 hours of life and until vascularization of the retina was complete. Oral vitamin E was provided as an emulsion of dl-alpha-tocopheryl acetate in gelatin, silicon dioxide, polysorbate 80, and medium chain triglycerides; the osmolality was 150 mOsm/kg. Among the 168 patients entered into the study, 79 were allocated to the treatment group and 89 to the control group. Average gestational ages were  $28.7 \pm 1.9$  and  $29.4 \pm 2.0$  weeks, respectively, in the experimental group and in the control group, and average birth weights were, respectively,  $1091 \pm 233$  and  $1113 \pm 245$  g. Outcome variables included (1) mortality (Pedi-

atrics 1984, Table 4 and Figure 1) and (2) among those surviving ten weeks: bronchopulmonary dysplasia, patent ductus arteriosus, sepsis, periventricular-intraventricular hemorrhage, retrolental fibroplasia, necrotizing enterocolitis, number of transfusions and amount of blood transfused (primary reference).

**Jansson 1978** is a randomized trial assessing the effect of iron and vitamin E on hematologic parameters in preterm infants. Entry criterion was a birth weight less than 2500 g. Patients who died before ten weeks ( $n = 33$ ) were excluded from all other outcomes. Patients were randomly allocated into three groups. Group I (control) received ferrous succinate starting at three weeks of age (elemental iron 2-3 mg/kg/day); group II received dl-alpha-tocopheryl acetate (E-vitamin®, AB ACO, dispersible in lipid solutions) 15 mg/day started at 10 days and ferrous succinate started at 3 weeks; and group III received tocopheryl acetate 15 mg/day started at 10 days and ferrous succinate started at 10 weeks. Among the 57 enrolled patients, 24 were allocated to Group I, 17 to group II and 16 to group III. For this systematic review we compared groups I and II, in which iron was initiated at the same postnatal age. Average birth weights in groups I (control) and II (treatment) were 1899 and 1767 g for those < 2 kg and 2135 and 2330 g for those 2.000-2.499 kg, respectively (variability not provided). Mean gestational ages were, respectively, 34.6 and 35 weeks for those with a birth weight less than 2 kg, and 37.5 and 36.4 weeks for those with a birth weight between 2.000 and 2.499 kg. Outcome variables included hemoglobin concentration, reticulocyte count and platelet count.

**Johnson 1989** is a double-blind randomized trial assessing the effect of parenteral vitamin E (under a FDA-approved IND) on retinopathy of prematurity in preterm infants. Entry criteria included: (1) birth weight equal to or less than 2000 g or (2) gestational age equal to or less than 36 weeks and oxygen treatment required; informed consent, and admission within 5 days of age. Treatment included: (1) for infants receiving intravenous feeding: 15 mg/kg vitamin E intramuscularly and 15 mg/kg intravenously (given at a 1:100 dilution over an 8-hour period) at study admission, followed by 15 mg/kg intravenously the next day; (2) for infants receiving oral feedings: 15 mg/kg vitamin E intramuscularly and 100 mg/kg/day divided in aliquots in the feeds. Subsequent investigational vitamin E dosage was provided until retinal vascularization was complete or active ROP had subsided, to maintain serum tocopherol level of 5 mg/dl. Parenteral vitamin E was provided as free dl-alpha-tocopherol 50 mg/ml (55 IU/ml) emulsified with Emulfor E1-620. Enteral vitamin E was provided as free dl-alpha tocopherol 50 mg/ml with 180 mg/ml polysorbate 80, and 700 mg/ml propylene glycol 80. Controls received placebo both for oral and parenteral preparations, with dosage adjustments to mimic those in the control group. In infants in whom severe ROP had developed, the study medication was replaced with vitamin E. Among 914 infants enrolled into the study, 454 were allocated to the treatment group and 460 to the control group. Average birth weight was  $1461 \pm 457$  g in the treatment group and  $1444 \pm 439$  g



in the controls. Average gestational age was  $31.5 \pm 2.7$  weeks in the treatment group and  $31.6 \pm 2.8$  weeks in the controls. Age at study entry was  $1.6 \pm 1.2$  days for patients in the treatment group and  $1.5 \pm 1.0$  days for controls. The only outcome variables available in the whole study population (Birth Defects 1988, page 226) was intraventricular hemorrhage. Examination for the presence of retinopathy of prematurity was done in 755 patients. Outcome variables available among the 545 infants with birth weight less than or equal to 1500 g (Pediatrics 1985 & 1989) included mortality, bronchopulmonary dysplasia (diagnosed radiographically), patent ductus arteriosus, patent ductus arteriosus requiring treatment, sepsis after study entry, intraventricular hemorrhage (Birth Defects page 226), retinopathy of prematurity, and necrotizing enterocolitis. Outcome variables available in subsets of the population included sepsis after study entry among very low birth weight infants treated for more than one week, bilirubin (excluding hemolytic anemia, polycythemia, and prior transfusion: Pediatrics 1980), and amount of blood transfusion (subset of very low birth weight infants: Pediatrics 1989).

Melhorn 1971 is a randomized trial assessing the effect of iron and vitamin E on hemoglobin concentration in infants admitted to the premature nursery. Exclusion criteria included: either small or large for gestational age, hemoglobin concentration  $< 14$  g/dl in the first 24 hours of life, blood group incompatibility, hemoglobinopathy, red blood cell enzyme deficiency, infection, defects requiring surgical intervention. After stratification for gestational age and birth weight within the first 48 hours of life, patients were randomized to one of four groups: Group I: no supplement (control); Group II: vitamin E: alpha tocopheryl acetate 25 units/day orally from the eighth to the forty-second day of life; group III: iron from the fifteenth to forty-second day of life: 10 mg/day if weight  $< 1500$  g, 15 mg/day if weight 1501-2000 g, 20 mg/day if weight  $> 2001$  g; group IV: iron and vitamin E. Among the 234 enrolled into the study, data are available in 186, including 45 randomized to group I, 47 to group II, 44 to group III and 50 to group IV. In category A, mean gestational age in each ranged from 30 to 31 weeks and mean birth weight ranged from 1170 grams to 1280 grams. In category B, mean gestational age was 34 weeks in each group, and mean birth weight ranged from 1700 grams to 1775 grams. In category C, mean gestational age in each group ranged from 37 to 38 weeks and mean birth weight from 2168 grams to 2243 grams. For this review, the effect of vitamin E was assessed by comparing group II with group I (no iron) and group IV with group III (iron). Outcome variables in categories A and B included hemoglobin at ten weeks of age and reticulocyte count.

Pathak 2003 is a double-blind randomized trial assessing the effect of enteral administration of vitamin E 50 IU/day on hemoglobin concentration and reticulocyte count in very low birth weight infants receiving erythropoietin and iron. Entry criteria included: gestational age less than or equal to 32 weeks, birth weight less than or equal to 1250 grams, clinically stable (less than 7.5 ml/week

phlebotomy, oxygen requirement less than or equal to 35%, intermittent mandatory ventilation less than or equal to 25 breaths per minute, and mean airway pressure less than or equal to 8 cm of water). Exclusion criteria included: a disease involving any major organ system, life-threatening congenital malformations or sepsis, isoimmunization with clinically apparent hemolytic anemia, hemolytic disorder, and intraventricular hemorrhage grade III or greater. Controls received placebo. All patients entered into the study were receiving erythropoietin 100 units/kg/day five days a week for eight weeks or until discharge, whichever came first. Infants fed intravenously received a multivitamin preparation (MVI Pediatric®) containing 1.4 mg alpha-tocopheryl acetate/ml at a dose of 1.5 ml/day and 3.25 ml/day to infants weighing  $< 1$  kg and  $> 1$  kg, respectively. All infants fed enterally at least 40 ml/kg/day received oral iron 6 mg/kg/day and 1 ml of a multivitamin preparation containing 5 U/ml vitamin E. Among 30 patients entered into the study, 15 were allocated to the treatment group and 15 to the control group. Average birth weights in the treatment group and in the control group were, respectively,  $928 \pm 170$  grams and  $899 \pm 159$  grams, average gestational ages were, respectively,  $27.9 \pm 1.9$  and  $27.9 \pm 1.5$  weeks, and postnatal ages at the time of study entry were, respectively,  $24.4 \pm 15.5$  days and  $28.1 \pm 10.1$  days. Outcome variables included mortality, patent ductus arteriosus requiring treatment, sepsis, necrotizing enterocolitis, hemoglobin concentration, reticulocyte count, number of transfusions, and total volume of blood transfused.

Phelps 1987a is a double-blind randomized trial assessing the effect of intravenous administration of a dose of 20 mg/kg of an investigational drug [nonesterified dl-alpha-tocopherol in alcohol or its vehicle (10% ethyl alcohol, 10% propylene glycol, 10% Emulphor, 1% benzyl alcohol, and buffering salts)] provided within 24 hours of birth and repeated on day two (and sometimes day three). Entry criteria included: birth weight less than 1500 g or gestational age less than 33 weeks, less than 24 hours of age, free from recognized congenital anomalies of the eyes or congenital anomalies incompatible with survival, and informed consent. Doses were adjusted to achieve plasma tocopherol levels of 3-3.5 mg/dl. Average daily intramuscular dose was  $14.4 \pm 4.7$  mg/kg/day during the first week, and ranged between 4.1 and 7.0 mg/kg/day during the subsequent weeks. Infants fed enterally received enteral vitamin E (free tocopherol), which was started at a dose of 100 mg/kg/day and adjusted according to the serum level. Supplemental intramuscular injections were given to infants with plasma levels lower than 2.5 mg/dl despite oral doses exceeding 200 mg/kg/day. Average oral dose (after the initial parenteral administration) was  $69 \pm 66$  mg/kg/day; 56 of 108 patients with oral vitamin E administration received intramuscular supplementation (one to four doses). Control infants received placebo. All infants fed intravenously received 1.2 mg/kg/day of tocopheryl acetate in standard multivitamin supplements. Controls received therapeutic vitamin E if they developed hemolytic anemia associated with a plasma level of tocopherol less than 0.5 mg/dl. Infants requir-

ing surgery or chest tube placement were given vitamin A 2500 IU/day for a week. The total number of patients entered into the study was 287, including 140 in the treatment group and 147 in the control group. Average birth weights in the treatment group and in the control group were, respectively, 1181±307 grams and 1205±319 grams, and average gestational ages were, respectively, 29.5±2.5 weeks and 29.9±1.5 weeks. Outcome variables included (1) among all infants: mortality, sepsis after 48 hours, periventricular-intraventricular hemorrhage and necrotizing enterocolitis, (2) among 232 infants with ophthalmologic examination: retinal hemorrhage, and (3) among 196 surviving infants: retinopathy of prematurity.

**Rönnholm 1989** is a randomized trial assessing the effect of intramuscular administration of dU-rac-alpha-tocopheryl acetate 20 mg/kg/day (Ephynal®, Hoffmann-La Roche) during the first three days of life in preterm infants. The entry criterion was a birth weight less than or equal to 1520 g. Patients in both groups received oral administration of water soluble vitamin E dl-alpha-tocopheropolyethylene glycolol 1000-succinate (part of a multi-vitamin preparation, Ekavit®l, Orion Corp Ltd) in increasing doses of 1.6 mg/day on day 3 to 10 mg/day at age 2-12 weeks. Controls received oral vitamin E only. Iron supplementation was started gradually at two weeks of age, and increased until six weeks of age to reach four mg/kg/day if birth weight was ≤ 1000 grams and 3 mg/kg/day if birth weight was > 1000 grams. Vitamin A was supplemented as retinol palmitate (1500 IU/day), starting at twelve weeks of postnatal age, or approximately 42 weeks of postmenstrual age, i.e., after all outcomes of interest had already been assessed. Patients were also randomly supplemented with human milk protein, medium-chain triglycerides, both or neither. The total number of patients entered into the study was 54, including 23 allocated to the treatment group and 31 to the control group. Absolutely no data are provided about the three patients who died from respiratory distress syndrome or from cerebral hemorrhage. Average birth weights in the treatment group and in the control group were, respectively, 1153±245 grams and 1222±228 grams, and average gestational ages were, respectively, 29.9±1.9 weeks and 30.4±2.1 weeks. Outcome variables among the 51 survivors included bronchopulmonary dysplasia, intraventricular hemorrhage, retrolental fibroplasia, and necrotizing enterocolitis.

**Rudolph 1989** is a randomized controlled trial assessing the effect of intramuscular administration of dl-alpha-tocopherol (Hoffman-La Roche) at dose of 25 mg/kg within 12 hours of birth, with repeated injections 24 hours later, and at 4, 5, 10, 20 and 30 days of age, yielding a total cumulative dose of 175 mg/kg on neonatal outcome. Entry criteria included: preterm delivery, birth weight 750-1500 g, and intensive care. Controls received no vitamin E supplementation. All infants fed intravenously received 2.5 IU vitamin E per liter of parenteral solution. Among the 29 patients entered into the study, thirteen were allocated to the treatment group and sixteen to the control group. Average birth weights in

the treatment group and in the control group were, respectively, 1202±198 grams and 1187±198 grams, and average gestational ages were, respectively, 30.7±2.3 weeks and 30.5±1.6 weeks. Outcome variables included mortality, patent ductus arteriosus (assessed clinically), severe retinopathy of prematurity and necrotizing enterocolitis.

**Saldanha 1982** is a randomized controlled trial assessing the effects on intramuscular administration of 25 mg of dl-alpha-tocopherol (Hoffman-La Roche) upon entry into the study and daily thereafter until serum tocopherol level rose above 2-4 mg/dl or until oxygen was no longer required. Entry criteria included gestational age less than 37 weeks, hyaline membrane disease, oxygen requirement at least 60% in first 24 hours or 80% thereafter, and informed consent. Exclusion criteria included cyanotic heart disease, multiple malformations, and known infectious disease. Controls received no injection. The total number of patients entered into the study was 44, including 21 in the treatment group and 23 in the control group. Average birth weights in the treatment group and in the control group were, respectively, 1458±491 grams and 1554±557 grams. Average gestational ages among patients surviving ten days were, respectively, 32.4±2.1 weeks and 32.9±2.9 weeks. Outcome variables among patients surviving ten days or more included: bronchopulmonary dysplasia and patent ductus arteriosus (diagnosed clinically).

**Schiller 1980** is a randomized trial assessing the effect of intramuscular administration of dl-alpha-tocopherol (175 mg/kg over a 30-day period) on patent ductus arteriosus. Entry criteria were: preterm infant, and birth weight < 1750 g. Time of onset is not provided. Controls did not receive any injection. Among the 29 infants entered into the study, sixteen were allocated to the treatment group, and thirteen to the control group. The outcome variable was patent ductus arteriosus.

**Sinha 1987** is a randomized trial assessing the effect of intramuscular administration of alpha-tocopheryl acetate (Ephynal®, Hoffman-La Roche) 20 mg/kg daily for three doses commencing within two hours after randomization (first day of life). Entry criteria included gestational age equal or less than 32 weeks, admitted from January 1984 to September 1985. No exclusion criteria were used before randomization; however, patients randomized before delivery and found after birth to have lethal malformations were excluded from the study. Controls received no placebo. The mothers of some infants were part of another randomized trial: they were allocated either to vitamin E 400 mg every 4-6 hours or to placebo capsules during preterm labor. Among the 231 patients entered into the study, no data are provided on the three infants with lethal malformations, so that the total number of patients retained in the study is 228 (presumably 115 treated patients and 113 controls, based on totals in Table II plus numbers of excluded patients in the second paragraph of the discussion). Only partial data are provided in 18 patients with a hemorrhage on the initial ultrasonography obtained within two hours of life or (if out born) upon admission to the unit. In the manuscript, several data are presented only in

the 210 patients with negative initial scan (102 patients in the treatment group and 108 in the control group), including birth weights in the treatment group and in the control group (respectively, 1273±315 grams and 1214±346 grams), gestational ages (respectively, 29.3±2.0 weeks and 28.8±2.2 weeks), and complete information about the classification of the intracranial hemorrhage. The authors used a classification in 3 grades; therefore, grade 3 was re-coded into Papile's grade IV (intraparenchymal hemorrhage). Outcome variables available in all patients included mortality, periventricular-intraventricular hemorrhage (adding numbers in Table II and those in the second paragraph of the discussion), necrotizing enterocolitis, and reaction at site of injection.

[Smith 1985](#) is a double-blind randomized trial assessing the effect of oral administration of dl-alpha-tocopheryl polyethylene glycol-succinate (Mead Johnson) 50 mg/day once a day for three consecutive days; the first dose was given before 24 hours of life. Entry criteria included: gestational age 30-36 weeks, birth weight 970-2610 g, healthy, lack of pulmonary disease or oxygen requirement, no ABO or Rh isoimmunization, and no other sources of bilirubin production, such as hematoma or bruising. The only exclusion criterion was infection. Control patients received placebo. All infants were fed either breast milk or a proprietary formula without iron (vitamin E contents ranging from 12 to 25 IU/L). Decisions regarding phototherapy were made by staff physicians who were unaware of the study results. Among 30 patients entered into the study, seventeen were allocated to the treatment group and thirteen to the control group. Average birth weights were 1.79±0.38 kg in the treatment group and 1.83±0.33 kg in the control group; average gestational ages were 32.6±1.6 weeks and 33.4±1.5 weeks, respectively. Outcome variables included bilirubin concentration and hemoglobin concentration.

[Zipursky 1987](#) is a double-blind randomized trial assessing the effect of enteral (gavage) supplementation of 25 IU vitamin E daily provided as 16 mg dl-alpha-tocopherol (Hoffman-La Roche) for six weeks in preterm infants smaller than 1500 g on anemia, coagulation tests and serum tocopherol levels. Entry criteria included birth weight < 1500 g, expected survival greater than 48 hours, and informed consent. Exclusion criteria included major congenital anomalies and Rhesus hemolytic disease. Infants in the control group received placebo (Tween 80). Age at entry into the trial was 2.7±3 days in treatment group and 2.9±2 days in control group. Infants in both groups also received recommended amounts of vitamin E, either in breast milk (5.4 IU/L and 0.8 mg/g of PUFA), SMA 20 (10 IU/L or 1.3 mg/g of PUFA) or SMA 24 (12 IU/L or 1.3 mg/g of PUFA). The range of PUFA content in milk used was 4-6 g/L. No added iron was provided, although SMA 20 and SMA 24 contained, respectively, 12.7 and 15.2 mg/L of iron sulfate. Individual or group amounts of feeding are not provided, so that total amount of iron cannot be calculated. The total number of patients is not the same in the two follow-up manuscripts (266 in Milner 1981 and 268 in Watts 1991). Assuming that these differences represent loss to follow-up (two patients lost to follow-

up acknowledged in Milner 1981), the total number of patients is presumed to be 269 infants entered into the study, with 135 allocated to the treatment group and 134 to the control group. Average birth weights were 1149±244 g and 1158±251 g in the treatment group and in the control group, respectively, and average gestational ages were 29.2±2.7 and 29.1±2.7 weeks, respectively. Mean age at entry into the trial was 2.7±3 days in the treatment group and 2.9±2 days in the control group. Baseline characteristics (number of infants < 1000 g, percentage of infants with severe illness) were similar in the two groups. Outcome variables included mortality and stages III or IV bronchopulmonary dysplasia (defined, respectively, by bilateral cystic lesions without or with fibrosis) and retrolental fibroplasia, and among specific subsets, hemoglobin concentration, reticulocyte count, platelet count, and coagulation tests.

2. Vitamin E versus another type or route of vitamin E formulation  
Only one study was in this group. [Bonati 1991](#) compared between two formulations of intramuscular vitamin E the amount of drug absorption and clinical outcomes in live born infants with gestational age less or equal to 32 weeks. Entry criteria included: live born infant, gestational age equal or less than 32 weeks, no malformations, born in participating centers over 3 months, and admitted to a neonatal intensive care within two hours of birth. Patients received three daily doses of 20 mg/kg of vitamin E starting at 8 hours of life. Infants were randomly allocated to the treatment group, receiving dl-alpha-tocopheryl acetate as an aqueous colloidal solution (Ephynal®, Hoffmann-La Roche, Basel, Switzerland), or to the control group, receiving alpha-tocopherol in olive oil solution (Evio Forte®, Bracco, Milan). The exact amounts of vitamin E administered enterally and by transfusion are not provided. Infants received 2-98 ml/kg/day of enteral feeding, including breast milk (vitamin E content 1.11±0.53 mg/100 ml) or formula (vitamin E content 0.23±0.08 mg/100 ml). Among 50 enrolled patients, 44 (22 in each group) completed the study. Birth weights ranged from 670 g to 1800 g with an average of 1217±311 g. Average gestational age was 29.0±2.5 weeks.

## Risk of bias in included studies

Among the 26 randomized clinical trials selected for this systematic review, ten were double-blinded.

### 1. Vitamin E versus placebo

[Chiswick 1982](#): No information is provided about the method of randomization or about blinding of allocation. Since patients in the control group did not receive intramuscular injection of vitamin E, intervention and outcome were not blinded. Although information is provided on all patients entered into the study, the exact number of patients with intraventricular hemorrhage is not provided, because not all patients had a computerized tomography or an autopsy. The authors assumed that all patients who died had an intraventricular hemorrhage; in one case, neither computerized tomography nor autopsy was available to confirm this assumption.

For the purpose of this review, only confirmed cases of intraventricular hemorrhage were used.

**Chiswick 1983:** No information is provided about the method of randomization or about blinding of allocation. Since patients in the control group did not receive intramuscular injection of vitamin E, intervention and outcome were not blinded. The number of patients with intraventricular hemorrhage may have been underestimated because not all patients had ultrasonograms performed after 3 days of age.

**Cruz 1983:** No information is provided about the method of randomization or about blinding of allocation. Since patients in the control group did not receive intramuscular injection of vitamin E, intervention and outcome were not blinded. Follow-up was complete.

**Ehrenkranz 1982** is a double-blind randomized controlled trial. The method of randomization is not provided. Allocation, intervention and outcome were blinded. Follow-up was complete; however, assessment for intraventricular hemorrhage by ultrasonogram or computerized tomography was obtained in only 27 of 47 patients in the experimental group and 39 of 53 in the control group. Therefore, the rate of intraventricular hemorrhage may have been underestimated.

**Ferlin 1998** is a randomized controlled trial with four parallel arms. The methods for randomization and blinding of allocation are not provided. Intervention and outcome were blinded. Completeness of follow-up is unclear; by design, only patients with regular follow-up visits after discharge were included.

**Finer 1982:** For randomization the authors used sealed envelopes, and stratification by birth weight and by severity of respiratory distress (requirement for oxygen and endotracheal intubation). Since controls did not receive placebo injections, intervention was not blinded. In contrast, the main outcome variable for the trial (retrolental fibroplasia) was blinded. Most data are available only for the 99 infants who completed the trial, i.e., survived for at least one month.

**Fischer 1987** is a double-blind randomized trial. The method of randomization is not provided. Intervention and outcome were blinded. Follow-up was complete.

**Fish 1990** is a double-blind randomized trial. Randomization was performed by the pharmacy after stratification by birth weight. Although a placebo was given to the control group, the intervention was not entirely blinded because tocopherol levels were available to the clinicians, who were adjusting the dose accordingly after day seven of life. Two infants were excluded from statistical analysis because of initial inapparent structural anomalies (congenital heart disease and hydranencephaly). Outcome was blinded.

**Graeber 1977:** The method of randomization is not provided. Intervention and outcome were not blinded. Follow-up was complete.

**Gross 1977:** The method of randomization is not provided. Intervention and outcome were not blinded. Follow-up was complete.

**Gross 1979:** The method of randomization is not provided; how-

ever, randomization was stratified by weight (1000-1500 g and 1501-2000 g). Neither intervention, nor outcome were blinded. Follow-up was complete.

**Hittner 1981** is a double-blind randomized trial. Randomization was performed using a random-number table, after stratification by weight. Allocation, intervention and outcome were blinded. Follow-up was not complete: information on 49 patients is incomplete. One patient with necrotizing enterocolitis was excluded (no information on treatment allocation), and one patient was excluded for necrotizing enterocolitis preventing oral administration of vitamin E (n=1). Patients who died before four weeks (n=48) were excluded from all other outcomes.

**Hittner 1984** is a double-masked randomized trial. Randomization was conducted using a random-number table, after stratification by weight. Allocation, intervention and outcome were blinded. Mortality was reported only until ten weeks of life. None of the other outcomes are reported for the 33 patients who died before 10 weeks.

**Jansson 1978:** The method of randomization was not provided; randomization was stratified by weight (1000-1999 and 2000-2499 g). Neither treatment allocation, nor intervention, nor outcome was blinded. All patients were followed.

**Johnson 1989** is a double-blind randomized controlled trial. The method of randomization is not provided. Randomization was stratified by hospital and by birth weight. Allocation, intervention and outcome were blinded. Complete data are available in only 755 of 914 enrolled.

**Melhorn 1971:** The method of randomization is not provided. Randomization was stratified by weight and gestational age. Data are provided on only 186 patients. Whether allocation was blinded is unclear. Neither intervention nor outcome were blinded.

**Pathak 2003** is a randomized double-blind trial. Randomization was done using sealed envelopes in the pharmacy. Allocation, intervention, and outcome were blinded. Follow-up was complete.

**Phelps 1987a** is a randomized double-blind trial. Randomization was performed using sealed envelopes stratified by study center, sex, and birth weight, opened at the pharmacy (center 1) or drug control center (center 2). Numbers were balanced by groups of eight. Multiple births were randomized separately so that one of each pair received placebo and one tocopherol. Allocation, intervention and outcome were blinded. Follow-up was complete for several neonatal outcomes. However retinal examinations were not obtained in 55 infants, including nine infants lost to follow-up and 46 who had died. Among the 80 infants who developed retinopathy of prematurity, 53 completed the study, eighteen were lost to follow-up and nine died with active retinopathy of prematurity.

**Rönnholm 1989:** The method of randomization is not provided, so that blinding of allocation cannot be assessed. Neither intervention, nor outcome was blinded. Three patients died of respiratory distress or cerebral hemorrhage and were excluded from the analysis.

**Rudolph 1989:** The method of randomization is not provided.

Blinding of allocation cannot be assessed. The intervention was not blinded, but the outcome, assessed by a cardiologist, was blinded. Follow-up was complete.

[Saldanha 1982](#): Randomization was performed by drawing of a card from a randomized deck. Neither allocation, nor intervention, nor outcome was blinded. Incomplete data provided on nine babies who died before 10 days of age.

[Schiller 1980](#): The method of randomization is not provided. Blinding of allocation cannot be assessed. The intervention was not blinded, whereas outcome was blinded. Whether follow-up was complete is unclear.

[Sinha 1987](#) is a randomized trial using sealed envelopes and thus allocation was blinded. However, controls did not receive a placebo, so that intervention was not blinded. Whether outcome was blinded is unclear. Three inborn infants randomized before birth had lethal major malformations and were excluded from the study. Eighteen infants had a periventricular-intraventricular hemorrhage on the initial scan; for these infants, only partial information is provided about the severity of the bleeding during the study.

[Smith 1985](#) is a randomized double-blind trial, so that allocation, intervention and outcome should be blinded; nevertheless, no information is provided about the method of randomization. Follow-up was complete.

[Zipursky 1987](#) is a double-blind randomized controlled trial in which the authors used a computerized randomization generated in the pharmacy and stratified by birth weight and by severity of illness. Allocation, intervention and outcome were blinded. Information on chronic lung disease was available in 266 of 269 enrolled infants, while only 225 infants had an eye examination. In the treatment group, hemoglobin levels, reticulocyte counts, and platelet counts were available in 44, 31, and 32 infants, respectively, at 6 weeks of age. In the control group, hemoglobin levels, reticulocyte counts, and platelet counts were available in 46, 33, and 36 infants, respectively, at 6 weeks.

2. Vitamin E versus another type or route of vitamin E formulation  
[Bonati 1991](#): No information is provided about method of randomization of the first baby within each center. Subsequent infants were given alternating medication, so that allocation, intervention and outcomes were not blinded. In each participating center, the first enrolled infant was randomly allocated to one of the two formulations; allocation was alternated in each subsequent infant. Among 50 patients in this study, only 44 completed the three-day schedule of vitamin E; no data are provided on the other infants. Outcome variables included mortality, patent ductus arteriosus, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, sepsis, phototherapy, exchange transfusion and tocopherol levels.

## Effects of interventions

No relevant data for the following subgroup analyses was found: gestational age  $\geq 29$  weeks, gestational age  $< 29$  weeks, parenteral vitamin E in colloidal form with polysorbate, selenium fortification, and vitamin E supplementation started after four weeks of life (although controls in [Pathak 2003](#) were started on placebo at an average age of 28 days).

### VITAMIN E VERSUS PLACEBO OR NO TREATMENT (COMPARISON 01):

#### Primary outcomes:

##### Mortality:

##### Mortality until discharge (Outcome 01.01):

Mortality was assessed in twelve studies, involving a total of 994 treated patients and 1034 controls. Vitamin E supplementation did not significantly affect mortality (typical estimate, relative risk [RR] 0.97, confidence interval [CI] 0.83, 1.14; risk difference [RD] -0.01, CI -0.04, +0.03).

Subgroup analyses: data available for analysis by birth weight (see section 01.02), by route of administration, total dose, serum level, onset and duration of therapy in the treatment group, by dose of vitamin E in the control group, and by intake of iron and PUFA. Vitamin E supplementation did not significantly affect mortality in any of the analyses.

##### Mortality until discharge among very low birth weight infants (Outcome 01.02):

Mortality was assessed in seven studies, involving a total of 628 treated patients and 648 controls. Vitamin E supplementation did not significantly affect mortality (typical estimate RR 0.97, CI 0.80, 1.16; RD -0.01, CI -0.05, +0.04).

Subgroup analyses: data available for analysis by birth weight, by route of administration, total dose, serum level, onset and duration of therapy in the treatment group, by dose of vitamin E in the control group, and by intake of iron, and PUFA. Vitamin E supplementation did not significantly affect mortality in any of the analyses.

#### COMBINED OUTCOMES:

No trial assessed combined outcome at eighteen months including mortality [mortality, bronchopulmonary dysplasia, blindness, mental retardation or cerebral palsy], nor combined outcome at 18 months excluding mortality [bronchopulmonary dysplasia, blindness, mental retardation or cerebral palsy].

#### Secondary outcomes:

##### Bronchopulmonary dysplasia:

##### Bronchopulmonary dysplasia (Outcome 01.03):

Bronchopulmonary dysplasia was assessed in six studies, involving a total number of 558 treated patients and 569 controls. Vitamin E supplementation did not significantly affect the risk of bronchopulmonary dysplasia (typical estimate RR 0.91, CI 0.73, 1.14; RD -0.02, CI -0.07, +0.03).

Subgroup analyses: data available for analysis by birth weight (see section 01.04), by route of administration, total dose, serum level, onset and duration of therapy in the treatment group, by dose of vitamin E in the control group, and by intake of iron, PUFA and



vitamin A. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Bronchopulmonary dysplasia among very low birth weight infants (Outcome 01.04):**

Bronchopulmonary dysplasia was assessed in four studies, involving a total number of 484 treated patients and 488 controls. Vitamin E supplementation did not significantly affect the risk of bronchopulmonary dysplasia (typical estimate RR 0.89, CI 0.71, 1.13; RD -0.02, CI -0.08, +0.03).

Subgroup analyses: data available for analysis by birth weight, by route of administration, total dose, serum level, onset and duration of therapy in the treatment group, by dose of vitamin E in the control group, and by intake of iron, PUFA and vitamin A. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Bronchopulmonary dysplasia among surviving patients (Outcome 01.05):**

This outcome was assessed in four studies, involving a total of 159 treated patients and 163 controls. Vitamin E supplementation did not significantly affect the risk of bronchopulmonary dysplasia (typical estimate RR 1.15, CI 0.84, 1.58; RD 0.04, CI -0.05, +0.13).

Subgroup analyses: data available for analysis by birth weight (see section 01.06), by route of administration, total dose, serum level, onset and duration of therapy in the treatment group, by dose of vitamin E in the control group, and by intake of iron. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Bronchopulmonary dysplasia among surviving very low birth weight infants (Outcome 01.06):**

This outcome was assessed in two studies, involving a total of 118 treated patients and 118 controls. Vitamin E supplementation did not significantly affect the risk of bronchopulmonary dysplasia (typical estimate RR 1.07, CI 0.70, 1.64; RD 0.02, CI -0.10, +0.13).

Subgroup analyses: data available for analysis by birth weight, by route of administration, total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Radiographic signs of bronchopulmonary dysplasia at six weeks to two months of age (Outcome 01.07):**

This outcome was analyzed in four studies, involving a total of 176 treated patients and 188 controls. Vitamin E did not significantly affect the risk of radiographic signs of bronchopulmonary dysplasia (typical estimate RR 0.99, CI 0.67, 1.46; RD 0.00, CI -0.09, +0.08).

Subgroup analyses: data available for analysis by birth weight (see section 01.08), by route of administration, total dose, serum level, onset and duration of therapy in the treatment group, by dose of vitamin E in the control group, and by intake of iron and

PUFA. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Radiographic signs of bronchopulmonary dysplasia at six weeks to two months of age among very low birth weight infants (Outcome 01.08):**

This outcome was analyzed in two studies, involving a total of 129 treated patients and 135 controls. Vitamin E did not significantly affect the risk of radiographic signs of bronchopulmonary dysplasia (typical estimate RR 0.95, CI 0.61, 1.47; RD -0.01, CI -0.11, +0.09).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, by dose of vitamin E in the control group, and by intake of iron and PUFA. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Patent ductus arteriosus:**

**Patent ductus arteriosus (Outcome 01.09):**

Patent ductus arteriosus was assessed in six studies, involving a total number of 481 treated patients and 495 controls. Vitamin E supplementation did not significantly affect the risk of patent ductus arteriosus (typical estimate RR 1.07, CI 0.93, 1.23; RD 0.03, CI -0.03, +0.09).

Subgroup analyses: data available for analysis by birth weight (see section 01.10), by route of administration, total dose, serum level, onset and duration of therapy in the treatment group, by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Patent ductus arteriosus among very low birth weight infants (Outcome 01.10):**

Patent ductus arteriosus was assessed in four studies, involving a total number of 418 treated patients and 429 controls. Vitamin E supplementation did not significantly affect the risk of patent ductus arteriosus (typical estimate RR 1.09, CI 0.93, 1.28; RD 0.04, CI -0.03, +0.10).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Patent ductus arteriosus among surviving patients (at ten days to ten weeks of age) (Outcome 01.11):**

This outcome was assessed in three, involving a total of 136 treated patients and 135 controls. Vitamin E supplementation did not significantly affect the risk of patent ductus arteriosus (typical estimate RR 0.98, CI 0.70, 1.38; RD -0.01, CI -0.11, +0.10).

Subgroup analyses: data available for analysis by birth weight (see section 01.12), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Patent ductus arteriosus among surviving very low birth weight infants (at ten days to ten weeks of age) (Outcome 01.12):**

This outcome was assessed in two studies, involving a total of 118 treated patients and 118 controls. Vitamin E supplementation did not significantly affect the risk of patent ductus arteriosus (typical estimate RR 0.85, CI 0.57, 1.27; RD -0.04, CI -0.15, +0.07).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Patent ductus arteriosus requiring treatment (Outcome 01.13):**

This outcome was assessed in three studies, involving a total number of 332 treated patients and 343 controls. Summary statistics showed no significant effect of vitamin E on patent ductus arteriosus (typical estimate RR 1.02, CI 0.79, 1.31; RD 0.00, CI -0.06, +0.07) with significant heterogeneity among studies both for RR (chi-square 5.99,  $p = 0.05$ ) and RD (chi-square 6.78,  $p = 0.034$ ).

Subgroup analyses: data available for analysis by birth weight (see section 01.14), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by iron intake. Vitamin E supplementation significantly reduced the risk for patent ductus arteriosus requiring therapy in the following subgroup analyses: (1) excluding intravenous therapy (01.13.06) (typical estimate RR 0.56, CI 0.32, 0.97; RD -0.17, CI -0.31, -0.02), (2) Duration of treatment greater than one week (01.13.12) (typical estimate RR 0.56, CI 0.32, 0.97; RD -0.17, CI -0.31, -0.02); (3) vitamin E intake greater than 10 mg/100 Kcal in the control group (01.13.14) in a single study (estimate RR 0.54, CI 0.31, 0.95; RD -0.22, CI -0.40, -0.03). [Ehrenkranz 1982](#) was the only study showing significant effect of vitamin E on this outcome; vitamin E was provided intramuscularly at high dose, starting within 48 hours and for more than one week in the treatment group, and vitamin E intake was greater than 10 mg/100 Kcal in the control group.

**Patent ductus arteriosus requiring treatment among very low birth weight infants (Outcome 01.14):**

This outcome was assessed in three studies, involving a total number of 285 treated patients and 290 controls. Summary statistics showed no significant effect of vitamin E on patent ductus arteriosus (typical estimate RR 1.20, CI 0.89, 1.60; RD 0.04, CI -0.03, +0.11).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by iron intake. Vitamin E did not significantly affect this outcome in any of the analyses.

**Sepsis****Sepsis after study entry (Outcome 01.15):**

Sepsis was assessed in four studies, involving a total number of 498 treated patients and 511 controls. Summary statistics showed a significant increase in risk of sepsis (typical estimate RR 1.52, CI 1.13, 2.04; RD 0.06, CI 0.02, 0.11). There was significant heterogeneity among studies for RD (chi-square 8.15,  $p = 0.04$ ) but not for RR (chi-square 2.89,  $p = 0.41$ ).

Subgroup analyses: data available for analysis by birth weight (see section 01.16), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by iron intake. Vitamin E significantly increased the risk of sepsis in the following subgroup analyses: (1) parenteral with or without enteral (01.13.03) or parenteral with hypertonic enteral formulation at pharmacologic dose (01.15.04) (typical estimate RR 1.57, CI 1.15, 2.14; RD 0.06, CI 0.02, 0.11); (2) Intravenous administration (01.15.05) (typical estimate RR 1.54, CI 1.07, 2.21; RD 0.05, CI 0.01, 0.10). However, there was significant heterogeneity among studies for RD (chi-square 6.25,  $p = 0.01$ ) but not for RR (chi-square 2.13,  $p = 0.14$ ); (3) Total dose of vitamin E in the treatment group greater than 30 IU/kg/day (01.15.07) (typical estimate RR 1.57, CI 1.15, 2.14; RD 0.06, CI 0.02, 0.11); (4) Serum tocopherol level in the treatment group greater than 3.5 mg/dl (01.15.09) (typical estimate RR 1.72, CI 1.24, 2.40; RD 0.10, CI 0.04, 0.15); (5) Onset of treatment within 48 hours of life (01.15.10) (typical estimate RR 1.57, CI 1.15, 2.14; RD 0.06, CI 0.02, 0.11); (6) Total dose of vitamin E in the control group equal to or less than 10 mg vit E/100 kcal (01.15.13) (typical estimate RR 1.48, CI 1.05, 2.08; RD 0.05, CI 0.01, 0.10).

**Sepsis after study entry among very low birth weight infants (Outcome 01.16):**

This outcome was assessed in four randomized trials, involving a total number of 400 treated patients and 407 controls. Summary statistics showed a significant increase in risk of sepsis (typical estimate RR 1.53, CI 1.13, 2.08; RD 0.07, CI 0.02, 0.13).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by iron intake. Vitamin E supplementation significantly increased the risk of sepsis in the following subgroups: (1) Birth weight less or equal to 1500 grams (01.16.02) (typical estimate RR 1.65, CI 1.13, 2.40; RD 0.08, CI 0.02, 0.14); (2) Subgroup characterized by parenteral with or without enteral (01.16.05), by total dose of vitamin E in the treatment group greater than 30 IU/kg/day (01.16.09) and by onset of therapy within 48 hours of life (01.16.12) (typical estimate RR 1.59, CI 1.15, 2.18; RD 0.08, CI 0.03, 0.13); (3) Intravenous vitamin E administration (01.16.07) (typical estimate RR 1.56, CI 1.07, 2.27; RD 0.07, CI 0.01, 0.12); (4) Serum level in the treatment group  $> 3.5$  mg/dl (01.16.11) (typical estimate RR 1.72, CI 1.24, 2.40; RD 0.10, CI 0.04, 0.15); and (5) total dose of vitamin E in the control group  $\leq 10$  mg/100 kcal (01.16.15) (typical es-

typical estimate RR 1.49, CI 1.04, 2.13; RD 0.06, CI 0.01, 0.12).

**Sepsis after study entry among very low birth weight infants treated for more than one week (Outcome 01.17):**

This outcome was assessed in four randomized trials, involving a total number of 362 treated patients and 364 controls. Summary statistics showed a significant increase in risk of sepsis (typical estimate RR 1.63, CI 1.17, 2.26; RD 0.08, CI 0.03, 0.13).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E and iron intake in the control group. Vitamin E supplementation significantly increased the risk of sepsis in the following subgroups: (1) Birth weight less or equal to 1500 grams (01.17.02) (typical estimate RR 1.79, CI 1.27, 2.53; RD 0.10, CI 0.04, 0.16); (2) Subgroup characterized by parenteral vitamin E with or without enteral administration (01.17.05), by total dose of vitamin E in the treatment group greater than 30 IU/kg/day (01.17.08) and by onset of therapy within 48 hours of life (01.17.11) (typical estimate RR 1.70, CI 1.20, 2.41; RD 0.08, CI 0.03, 0.14); (3) Intravenous vitamin E administration (01.17.06) (typical estimate RR 1.72, CI 1.11, 2.66; RD 0.07, CI 0.02, 0.13); (4) Serum level in the treatment group > 3.5 mg/dl (01.17.10) (typical estimate RR 1.90, CI 1.31, 2.75; RD 0.11, CI 0.05, 0.16); and (5) total dose of vitamin E in the control group ≤ 10 mg/100 kcal (01.17.13) (typical estimate RR 1.61, CI 1.08, 2.41; RD 0.07, CI 0.02, 0.13).

**Sepsis among surviving very low birth weight infants (Outcome 01.18):**

This outcome was assessed in two trials, involving 143 treated patients and 141 controls. Summary statistics showed no significant effect of vitamin E on sepsis (typical estimate RR 0.88, CI 0.48, 1.62; RD -0.02, CI -0.09, +0.06).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Germinal matrix/intraventricular hemorrhage**

**Germinal matrix/intraventricular hemorrhage (Papile's classification, grade I-IV) (Outcome 01.19):**

This outcome was assessed in seven studies involving 864 treated patients and 891 controls. Vitamin E supplementation significantly reduced the risk of germinal matrix-intraventricular hemorrhage (typical estimate RR 0.85, CI 0.73, 0.99; RD -0.04, CI -0.08, 0.00). There was significant heterogeneity among studies for RD (chi-square 17.81,  $p=0.0067$ ) but not for RR (chi-square 8.54,  $p=0.2$ ).

Subgroup analyses: data available for analysis by birth weight (see section 01.20), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementa-

tion significantly reduced the risk of hemorrhage in the following subgroups: (1) parenteral vitamin E administration with or without additional enteral vitamin E (01.19.03) (typical estimate RR 0.84, CI 0.72, 0.98; RD -0.04, CI -0.08, -0.01); (2) excluding intravenous vitamin E administration (01.19.06) (typical estimate RR 0.71, CI 0.58, 0.87; RD -0.14, CI -0.22, -0.06); (3) total dose of vitamin E in the treatment group less than or equal to 30 IU/kg/day (01.19.07) (typical estimate RR 0.65, CI 0.50, 0.85; RD -0.18, CI -0.29, -0.08); (4) onset of treatment within 48 hours of life (01.19.11), involving all patients in all studies for this outcome (for typical estimates see summary statistics); and (5) duration of vitamin E treatment less than or equal to one week (01.19.12) (typical estimate RR 0.65, CI 0.50, 0.85; RD -0.18, CI -0.29, -0.08).

**Germinal matrix/intraventricular hemorrhage (Papile's classification, grade I-IV) among very low birth weight infants (Outcome 01.20):**

This outcome was assessed in three studies involving 385 treated patients and 392 controls. Vitamin E did not significantly affect the risk of hemorrhage (typical estimate RR 0.94, CI 0.75, 1.18; RD -0.02, CI -0.07, +0.04).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Germinal matrix/intraventricular hemorrhage (Papile's classification, grade I-IV) among infants with negative initial ultrasound (Outcome 01.21):**

This outcome was assessed in a single study involving 102 treated patients and 108 controls. Vitamin E supplementation significantly reduced the risk for hemorrhage (estimate RR 0.57, CI 0.40, 0.80; RD -0.23, CI -0.36, -0.10).

**Germinal matrix/intraventricular hemorrhage (Papile's classification, grade I-IV) among survivors (Outcome 01.22):**

This outcome was assessed in three studies involving 166 treated patients and 169 controls. Vitamin E did not significantly affect the risk of hemorrhage (typical estimate RR 1.06, CI 0.70, 1.60; RD 0.01, CI -0.07, +0.10).

Subgroup analyses: data available for analysis by birth weight (see section 01.23), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Germinal matrix/intraventricular hemorrhage (Papile's classification, grade I-IV) among surviving low birth weight infants (Outcome 01.23):**

This outcome was assessed in two trials, involving 143 treated patients and 141 controls. Summary statistics showed no significant effect of vitamin E on germinal matrix/intraventricular hemorrhage (typical estimate RR 1.05, CI 0.69, 1.60; RD 0.01, CI -



0.09, +0.11).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

#### **Severe intraventricular hemorrhage (grade III or IV) (Outcome 01.24):**

This outcome was assessed in three studies, involving a total of 315 treated patients and 329 controls. Vitamin E supplementation did not significantly affect the risk of severe intraventricular hemorrhage (typical estimate RR 0.91, CI 0.60, 1.38; RD -0.01, CI -0.06, +0.04). There was significant heterogeneity among studies both for RR and RD (chi-square 6.98,  $p=0.03$ ).

Subgroup analyses: data available for analysis by birth weight (see section 01.25), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

#### **Severe intraventricular hemorrhage (grade III or IV) among very low birth weight infants (Outcome 01.25):**

This outcome was assessed in two studies, involving a total of 213 treated patients and 221 controls. Vitamin E supplementation did not significantly affect the risk of severe intraventricular hemorrhage (typical estimate RR 1.03, CI 0.67, 1.60; RD +0.01, CI -0.06, +0.07). There was significant heterogeneity among studies both for RR (chi-square 4.80,  $p=0.029$ ) and RD (chi-square 4.89,  $p=0.027$ ).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

#### **Severe intraventricular hemorrhage (grade III or IV) among surviving very low birth weight infants (Outcome 01.26):**

This outcome was analyzed in three studies, involving a total of 158 treated patients and 162 controls. Vitamin E supplementation did not significantly affect the risk of hemorrhage (typical estimate RR 0.76, CI 0.41, 1.39; RD -0.03, CI -0.10, +0.04 with significant heterogeneity among the studies for RD (chi-square 7.48,  $p=0.024$ ).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Subgroup analysis showed that vitamin E supplementation significantly reduced the risk of hemorrhage (1) in the subgroup of patients with birth weight less than 1000 grams (01.26.03) (typical estimate RR 0.31, CI 0.10, 0.92; RD -0.13, CI -0.24, -0.02), and (2) in that with serum levels greater than 3.5 mg/dl (01.26.11) (estimate RR 0.20, CI 0.05, 0.85; RD 0.20, CI 0.05, 0.85).

#### **Parenchymal brain hemorrhage**

##### **Parenchymal brain hemorrhage (grade IV) (Outcome 01.27):**

This outcome was assessed in two studies, involving 242 treated patients and 255 controls. Meta-analysis showed no significant overall effect of vitamin E on the risk of hemorrhage (typical estimate RR 1.35, CI 0.69, 2.67; RD 0.02, CI -0.02, +0.06) but showed substantial heterogeneity between the two studies both for RR (chi-square 5.31,  $p=0.021$ ) and RD (chi-square 7.73,  $p=0.0054$ ).

Subgroup analysis: data available for analysis by birth weight (see section 01.28), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Subgroup analysis suggests that the significant difference in results between the two studies could be attributed to dose (01.27.06-07), duration (01.27.10-11) and type of administration (01.27.03-05): [Phelps 1987a](#) used high-dose, intravenous and prolonged administration of vitamin E, in contrast with [Sinha 1987](#), which used low-dose, intramuscular vitamin E for less than one week.

##### **Parenchymal brain hemorrhage (grade IV) among very low birth weight infants (Outcome 01.28):**

This outcome was assessed in a single study, involving 42 treated patients and 43 controls. Vitamin E supplementation in infants less than 1000 grams significantly increased the risk for hemorrhage (estimate RR 9.21, CI 1.22, 69.58; RD 0.19, CI 0.06, 0.032). This study used high-dose, intravenous and prolonged administration of vitamin E.

##### **Parenchymal brain hemorrhage (grade IV) among patients with negative initial ultrasonogram (Outcome 01.29):**

This outcome was assessed in a single study, involving 102 treated patients and 108 controls. Vitamin E supplementation did not significantly affect the risk for hemorrhage (estimate RR 0.30, CI 0.06, 1.42; RD -0.05, CI -0.10, +0.01).

##### **Parenchymal brain hemorrhage (grade IV) among surviving very low birth weight infants (Outcome 01.30):**

This outcome was assessed in two studies, involving 118 treated patients and 118 controls. Vitamin E supplementation did not significantly affect the risk of hemorrhage (typical estimate RR 1.46, CI 0.46, 4.66; RD 0.02, CI -0.04, +0.07).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

#### **Retinopathy of prematurity or retrolental fibroplasia**

##### **Retinopathy of prematurity or retrolental fibroplasia (Outcome 01.31):**

This outcome was assessed in seven studies, involving 662 treated patients and 680 controls. Vitamin E supplementation did not significantly affect the risk of retinopathy of prematurity or retrolental fibroplasia (typical estimate RR 0.90, CI 0.75, 1.09; RD -

0.02, CI -0.07, +0.02).

Subgroup analyses: data available for analysis by birth weight (see section 01.32), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E and intake of iron, vitamin A and PUFA in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Retinopathy of prematurity or retrolental fibroplasia among very low birth weight infants (Outcome 01.32):**

This outcome was assessed in five studies, involving 489 treated patients and 486 controls. Vitamin E supplementation did not significantly affect the risk of retinopathy of prematurity or retrolental fibroplasia (typical estimate RR 0.88, CI 0.73, 1.07; RD -0.03, CI -0.09, +0.02).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron, vitamin A and PUFA. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Retinopathy of prematurity or retrolental fibroplasia among infants examined/survivors (Outcome 01.33):**

This outcome was assessed in eight studies, involving 821 treated patients and 845 controls. Vitamin E did not significantly affect the risk of retinopathy or prematurity or retrolental fibroplasia (typical estimate RR 0.90, CI 0.78, 1.03; RD -0.03, CI -0.07, +0.01).

Subgroup analyses: data available for analysis by birth weight (see section 01.34), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E did not significantly affect the risk of retinopathy or prematurity or retrolental fibroplasia in any of the analyses.

**Retinopathy of prematurity or retrolental fibroplasia among very low birth weight infants examined/survivors (Outcome 01.34):**

This outcome was assessed in seven studies, involving 540 treated patients and 550 controls. Vitamin E did not significantly affect the risk of retinopathy or prematurity or retrolental fibroplasia (typical estimate RR 0.94, CI 0.82, 1.07; RD -0.03, CI -0.08, +0.03).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E did not significantly affect the risk of retinopathy or prematurity or retrolental fibroplasia in any of the analyses.

**Severe retinopathy of prematurity or retrolental fibroplasia (grade III or worse) (Outcome 01.35):**

This outcome was assessed in six studies, involving a total of 767 treated patients and 798 controls. Vitamin E did not significantly affect the risk of severe retinopathy of prematurity or retrolental

fibroplasia in the treated group (typical estimate RR 0.72, CI 0.41, 1.25; RD -0.01, CI -0.03, +0.01).

Subgroup analyses: data available for analysis by birth weight (see section 01.36), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E significantly reduced the risk of retinopathy or prematurity or retrolental fibroplasia in the subgroup of studies with serum tocopherol level vitamin E in the treatment group greater than 3.5 mg/dl (01.35.10): typical estimate RR 0.39, CI 0.16, 1.00; RD -0.02, CI -0.04, 0.00.

**Severe retinopathy of prematurity or retrolental fibroplasia (grade III or worse) among very low birth weight infants (Outcome 01.36):**

This outcome was assessed in six studies, involving a total of 482 treated patients and 492 controls. Vitamin E did not significantly affect the risk of severe retinopathy of prematurity or retrolental fibroplasia in the treated group (typical estimate RR 0.59, CI 0.32, 1.08; RD -0.02, CI -0.05, 0.00).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E significantly reduced the risk of retinopathy or prematurity or retrolental fibroplasia (1) in the subgroup with birth weight equal to or less than 1500 grams (01.36.02) typical estimate RR 0.40, CI 0.18, 0.87; RD -0.03, CI -0.05, -0.01 and (2) in the subgroup with serum level in the treatment group greater than 3.5 mg/dl (01.36.12): typical estimate RR 0.34, CI 0.13, 0.87; RD -0.04, CI -0.07, 0.01.

**Severe retinopathy of prematurity or retrolental fibroplasia among infants examined (Outcome 01.37):**

This outcome was assessed in seven studies, involving a total of 783 treated patients and 804 controls. Vitamin E did not significantly affect the risk of severe retinopathy of prematurity or retrolental fibroplasia, typical estimate RR 0.67, CI 0.40, 1.12; RD -0.01, CI -0.03, 0.00.

Subgroup analyses: data available for analysis by birth weight (see section 01.38), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E significantly reduced the risk of retinopathy or prematurity or retrolental fibroplasia in the subgroup with serum tocopherol level vitamin greater than 3.5 mg/dl in the treatment group (01.37.11): typical estimate RR 0.39, CI 0.15, 0.98; RD -0.02, CI -0.04, 0.00.

**Severe retinopathy of prematurity or retrolental fibroplasia among very low birth weight infants examined (Outcome 01.38):**

This outcome was assessed in seven studies, involving a total of 525 treated patients and 537 controls. Vitamin E significantly reduced the risk of severe retinopathy of prematurity or retrolental

fibroplasia, typical estimate RR 0.58, CI 0.34, 1.00; RD -0.03, CI -0.05, 0.00.

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E significantly reduced the risk of retinopathy or prematurity or retrolental fibroplasia in the following subgroups: (1) birth weight  $\leq$  1500 grams (01.38.02) (typical estimate RR 0.44, CI 0.22, 0.85; RD -0.03, CI -0.05, -0.01); (2) serum level in the treatment group greater than 3.5 mg/dl (01.38.14) (typical estimate RR 0.34, CI 0.13, 0.88; RD -0.04, CI -0.07, -0.01); and (3) total dose of vitamin E in the control group equal to or less than 10 mg/100 kcal (01.38.18) (typical estimate RR 0.56, CI 0.31, 1.00; RD -0.03, CI -0.06, 0.00).

#### **Retinal detachment among surviving infants (Outcome 01.39):**

This outcome was assessed in three studies, involving a total of 215 treated patients and 217 controls. Vitamin E supplementation did not significantly affect the risk of retinal detachment, typical estimate RR 1.02, CI 0.06, 16.09; RD 0.00, CI -0.02, +0.02. However, the incidence of that complication was too low to reach any conclusion: it developed in only one patient in each group in a single study.

Subgroup analyses: data available for analysis by birth weight (see section 01.40), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E did not significantly affect the risk of retinal detachment in any of the analyses.

#### **Retinal detachment among surviving very low birth weight infants (Outcome 01.40):**

This outcome was assessed in three studies, involving a total of 160 patients in the treatment group and 161 in the control group. Vitamin E did not significantly affect this outcome, typical estimate RR 1.02, CI 0.07, 15.84; RD 0.00, CI -0.02, +0.02. However, the incidence of that complication was too low to reach any conclusion: it developed in only one patient in each group in a single study.

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E did not significantly affect the risk of retinal detachment in any of the analyses.

#### **Cicatricial retrolental fibroplasia, any stage, among patients examined after discharge (Outcome 01.41):**

This outcome was assessed in five studies, involving 530 patients in the treatment group and 522 in the control group. Vitamin E did not significantly affect this outcome (typical estimate RR 0.82, CI 0.52, 1.27; RD -0.01, CI -0.04, +0.02).

Subgroup analyses: data available for analysis by birth weight (see

section 01.42), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

#### **Cicatricial retrolental fibroplasia, any stage, among very low birth weight infants examined after discharge (Outcome 01.42):**

This outcome was assessed in five studies, involving 436 patients in the treatment group and 422 in the control group. Vitamin E did not significantly affect this outcome (typical estimate RR 0.75, CI 0.48, 1.15; RD -0.02, CI -0.06, +0.01).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

#### **Blindness from retrolental fibroplasia among very low birth weight infants examined (Outcome 01.43):**

This outcome was assessed in four studies, involving 231 treated patients and 236 controls. Vitamin E significantly decreased the risk of blindness, typical estimate, RR 0.29, CI 0.10, 0.88; RD -0.04, CI -0.08, -0.01).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E supplementation significantly reduced the risk of blindness (1) among four subgroups which involved all four studies: birth weight less or equal to 1500 grams (01.43.02), excluding intravenous vitamin E supplementation (01.43.08), onset of therapy within 48 hours of life (01.43.13) and duration of treatment greater than one week (01.43.14) (typical estimate identical to that for the main analysis), (2) in the subgroup with total dose of vitamin E in the control group equal to or less than 10 mg/100 kcal (01.43.15) (typical estimate RR 0.29, CI 0.10, 0.88; RD -0.05, CI -0.08, -0.01).

#### **Necrotizing enterocolitis**

##### **Necrotizing enterocolitis (Outcome 01.44):**

This outcome was assessed in eight studies, involving a total of 711 treated patients and 732 controls. Vitamin E supplementation did not significantly affect this outcome (typical estimate RR 1.37, CI 0.96, 1.95; RD 0.02, CI 0.00, +0.05).

Subgroup analyses: data available for analysis by birth weight (see section 01.45), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation significantly increased the risk for necrotizing enterocolitis among patients whose controls received less than or equal to 10 mg vit E/100 cal (01.44.15) (typical estimate RR 1.49, CI 1.03, 2.16; RD 0.03, CI 0.00, 0.06).

#### **Necrotizing enterocolitis among very low birth weight infants**

**(Outcome 01.45):**

This outcome was assessed in six studies, involving a total of 475 treated patients and 487 controls. Vitamin E supplementation did not significantly affect this outcome (typical estimate RR 1.29, CI 0.90, 1.87; RD 0.03, CI -0.01 +0.07).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Necrotizing enterocolitis among very low birth weight infants treated with vitamin E for more than one week (Outcome 01.46):**

This outcome was assessed in five studies, involving a total of 364 treated patients and 370 controls. Vitamin E supplementation did not significantly affect this outcome (typical estimate RR 1.51, CI 0.99, 2.30; RD 0.04, CI 0.00 +0.09).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation significantly increased the risk of necrotizing enterocolitis in the following subgroups: (1) birth weight less than or equal to 1500 grams (01.46.02): typical estimate RR 1.62, CI 1.04, 2.51; RD 0.05, CI 0.01, 0.10; and (2) serum tocopherol level in the treatment group greater than 3.5 mg/dl (01.46.12): typical estimate RR 1.60, CI 1.02, 2.52; RD 0.05, CI 0.00, 0.11.

**Necrotizing enterocolitis among survivors (Outcome 01.47):**

This outcome was assessed in two studies, involving a total of 91 treated patients and 95 controls. Vitamin E supplementation did not significantly affect this outcome (typical estimate RR 1.31, CI 0.31, 5.65,  $z = 0.37$ ,  $p = 0.7$ ; RD 0.01, CI -0.05, +0.07,  $z = 0.34$ ,  $p = 0.7$ ).

Subgroup analyses: data available for analysis by birth weight (see section 01.48), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Necrotizing enterocolitis among surviving very low birth weight infants (Outcome 01.48):**

This outcome was assessed in a single study, involving a total of 68 treated patients and 67 controls. Vitamin E supplementation did not significantly affect this outcome (estimate RR 1.31, CI 0.31, 5.65; RD 0.01, CI -0.06, +0.09).

**Serum bilirubin concentration****Serum bilirubin concentration on day 3-5 (Outcome 01.49):**

This outcome was assessed in three studies, involving a total of 54 treated patients and 44 controls. Meta-analysis showed no significant effect of vitamin E on this outcome (weighted mean difference [WMD] -0.30, CI -1.17, +0.57) but substantial heterogeneity

(chi-square 9.90,  $p = 0.0071$ ).

Subgroup analyses: data available for analysis by birth weight (see section 01.50), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation significantly decreased serum bilirubin concentration in the subgroup with total vitamin E dose in the treatment group greater than 30 IU/kg/day (01.49.07) (mean difference [MD] -1.30, CI -2.60, 0.00).

**Serum bilirubin concentration on day 3-5 in very low birth weight infants (Outcome 01.50):**

This outcome was assessed in two studies, involving a total of 27 treated patients and 21 controls. Meta-analysis showed a significant decrease in serum bilirubin (WMD -1.46, CI -2.58, -0.33).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation significantly decreased serum bilirubin concentration in the following subgroups: (1) Enteral (01.50.02) and total dose of vitamin E in the treatment group greater than 30 IU/kg/day (01.50.06) (MD -1.30, CI -2.60, 0.00); (2) Excluding intravenous (01.50.04), serum level in the treatment group equal to or less than 3.5 mg/dl (01.50.07), onset of treatment within 48 hours of life (01.49.08), duration of treatment less than or equal to one week (01.50.09) and total dose of vitamin E in the control group equal to or less than 10 mg/100 kcal (01.49.10), which included all patients from all studies (WMD -1.46, CI -2.58, -0.33).

**Serum bilirubin concentration on day 3-5 in a specific group (no hemolysis, no polycythemia, no prior transfusion) (Outcome 01.51):**

This outcome was assessed in a single study involving 31 treated patients and 31 controls. Vitamin E significantly increased serum bilirubin (MD =1.30, CI 0.20, 2.40).

**Hemoglobin concentration****Hemoglobin concentration (Outcome 01.52):**

Hemoglobin concentration was assessed in eight studies, involving 211 patients in the treatment group and 205 controls. Vitamin E supplementation significantly increased hemoglobin concentration (WMD 0.46 g/dl, CI 0.24, 0.69).

Subgroup analyses: data available for analysis by birth weight (see section 01.53), by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E supplementation significantly increased hemoglobin concentration in the following subgroups: (1) infants with birth weight > 1000 grams (01.52.02) (WMD 0.49, CI 0.20, 0.77), (2) enteral vitamin E supplementation (01.52.03) (WMD 0.48, CI 0.25, 0.71), (3) excluding intravenous vitamin E supplementation (01.52.05) (involving all available studies; typical estimate identical to the summary statistics for this outcome), (4) vitamin E dose less than or equal to 30 IU/kg/day (01.52.06)

(WMD 0.52, CI 0.29, 0.76), (5) serum tocopherol level in the treatment group less than or equal to 3.5 mg/dl (01.52.08) (WMD 0.47, CI 0.23, 0.71), (6) onset of treatment within 48 hours of life (01.52.09) (WMD 0.48, CI 0.21, 0.75), (7) onset of treatment after 48 hours of life (01.52.10) (WMD 0.44, CI 0.02, 0.85), (8) duration of treatment greater than one week (01.52.12) (WMD 0.54, CI 0.30, 0.77), (9) total dose of vitamin E in the control group equal to or less than 10 mg/100 kcal (01.52.13) (WMD 0.46, CI 0.24, 0.69), (10) iron supplementation in both groups (01.52.14) (WMD 0.57, CI 0.24, 0.91), and (11) iron supplementation in neither group (01.52.15) (WMD 0.47, CI 0.16, 0.78).

#### **Hemoglobin concentration in very low birth weight infants (Outcome 01.53):**

This outcome was analyzed in four studies, involving 102 treated infants and 94 controls. Meta-analysis showed a significant increase in hemoglobin, WMD 0.43 g/dl, CI 0.09, 0.77, with significant heterogeneity among studies (chi-square 10.38,  $p = 0.02$ ). Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E supplementation significantly increased hemoglobin concentration in the following subgroups: (1) Enteral vitamin E supplementation (01.53.02), excluding intravenous supplementation (01.53.03), serum tocopherol level vitamin E in the treatment group lower than or equal to 3.5 mg/dl (01.53.06), total dose of vitamin E in the control group equal to or less than 10 mg/100 kcal (01.53.11), all involving all subjects from all studies; (2) total dose of vitamin E in the treatment group less than or equal to 30 IU/kg/day (01.53.04) (WMD 0.53, CI 0.16, 0.90); (3) Onset of treatment in the treatment group within 48 hours of life (01.53.07) (WMD 0.42, CI 0.07, 0.78); (4) Duration of treatment greater than one week (01.53.10) (WMD 0.53, CI 0.17, 0.89); (5) Iron supplementation in both groups (01.53.12) (WMD 0.67, CI 0.23, 1.10); (6) Iron supplementation in neither group (01.53.13) (WMD 0.51, CI 0.17, 0.86).

#### **Reticulocyte count**

##### **Reticulocyte count (expressed in percent of total red blood cell count) (Outcome 01.54):**

This outcome was assessed in two studies, involving 102 treated patients and 99 controls. Meta-analysis showed that vitamin E supplementation significantly reduced reticulocyte count (WMD -1.66, CI -2.24, -1.07) and substantial heterogeneity among studies (chi-square 6.44,  $p = 0.011$ ).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron and PUFA. Vitamin E supplementation significantly reduced reticulocyte count in the following subgroups: (1) subgroups involving all patients from both studies: enteral (01.54.02), excluding intravenous vita-

min E supplementation (01.54.03), total dose of vitamin E in the treatment group equal to or less than 30 IU/kg/day (01.54.04), serum tocopherol level in the treatment group equal to or less than 3.5 mg/dl (01.54.05), onset of treatment within 48 hours of life (01.54.06), duration of treatment greater than one week (01.54.07), total dose of vitamin E in the control group less than or equal to 10 mg/100 kcal (01.54.08) (typical estimates identical to the summary statistics for this outcome); (2) iron supplementation in both groups (01.54.09) (MD -1.96, CI -2.89, -1.03); and (3) iron supplementation in neither group (01.54.10) (MD -1.47, CI -2.22, -0.72).

##### **Reticulocyte count (expressed in percent of total red blood cell count) in very low birth weight infants (Outcome 01.55):**

This outcome was assessed in a single study, involving 31 treated patients and 33 controls. Vitamin E supplementation did not significantly affect reticulocyte counts (MD -0.30, CI -1.50, +0.90).

##### **Absolute reticulocyte counts (expressed in million per liter) (Outcome 01.56):**

This outcome was assessed in two studies, involving 32 treated patients and 39 controls. Meta-analysis showed significant heterogeneity between the two studies (chi-square analysis 13.03,  $p = 0.0003$ ) and a significant reduction in reticulocyte count in the treated group (WMD -34.0, CI -46.2, -21.8,  $z = 5.48$ ,  $p < 0.00001$ ).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation significantly reduced reticulocyte count in the following subgroups, which involved all patients in both studies: enteral (01.56.02), excluding intravenous vitamin E supplementation (01.56.03), serum tocopherol level less than or equal to 3.5 mg/dl (01.56.05), onset of treatment after 48 hours of life (01.56.06), duration of treatment greater than one week (01.56.07), total dose of vitamin E intake in the control group equal to or less than 10 mg/100 kcal (01.56.08), and iron supplementation in both groups (01.56.09) (typical estimates identical to summary statistics for this outcome).

##### **Absolute reticulocyte counts (expressed in million per liter) in very low birth weight infants (Outcome 01.57):**

This outcome was assessed in a single study, involving 31 treated patients and 33 controls. Vitamin E supplementation significantly reduced absolute reticulocyte counts (MD -54.3, CI -70.7, -37.9).

#### **Blood transfusion**

##### **Number of transfusions (Outcome 01.58):**

This outcome was assessed in a single study involving 15 treated patients and 15 controls. Vitamin E supplementation did not significantly affect the number of transfusions (MD -0.20, CI -1.17, +0.77).

##### **Number of transfusions among survivors (Outcome 01.59):**

This outcome was assessed in a single study involving 68 treated

patients and 67 controls. Vitamin E supplementation did not significantly affect the number of transfusions (MD +1.20, CI -1.42, +3.82).

**Amount of blood transfused (ml per kg of body weight) among very low birth weight infants (Outcome 01.60):**

This outcome was assessed in two studies involving 223 treated patients and 231 controls. Vitamin E supplementation did not significantly affect the number of transfusions (WMD -0.5, CI -16.9, +15.9).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Amount of blood transfused among survivors (Outcome 01.61):**

This outcome was assessed in a single study involving 68 treated patients and 67 controls. Vitamin E supplementation did not significantly affect the number of transfusions (MD +18.1, CI -17.1, +53.3).

**Other outcomes**

**Platelet count (Outcome 01.62):**

Platelet counts were analyzed in two studies involving a total of 49 treated patients and 60 controls. Vitamin E supplementation did not significantly affect the platelet count (WMD -29.52, CI -88.81, +29.76).

Subgroup analyses: data available for analysis by birth weight, by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group, and by dose of vitamin E in the control group and by intake of iron. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Coagulation tests (Outcomes 01.63 - 01.65):**

The effects of vitamin E on coagulation tests were analyzed in one study involving 23 treated patients and 24 controls (Zipursky 1987), which used low dose enteral administration. Vitamin E administration did not significantly affect any of the coagulation tests, including prothrombin time, partial thromboplastin time, fibrinogen concentration and other factors not listed in this review.

**Retinal hemorrhage among very low birth weight infants examined/survivors (Outcome 01.66):**

This outcome was assessed in a single study, involving 111 treated patients and 121 controls, which used high-dose, intravenous administration of vitamin E. Vitamin E did not significantly affect the risk of retinal hemorrhage in the whole study population (estimate RR 2.18, CI 0.97, 4.89; RD 0.08, 0.16). Subgroup analysis among extremely low birth weight infants (n=85) showed that vitamin E significantly increased the risk of retinal hemorrhage (estimate RR 3.58, CI 1.28, 10.00; RD 0.24, CI 0.07, 0.41).

**Reaction at the site of injection (Outcome 01.67):**

This outcome was reported in two studies, involving 175 treated

patients and 182 controls. Meta-analysis showed no significant effect of vitamin E on this outcome (typical estimate RR 4.13, CI 0.47, 36.69; RD 0.02, CI -0.01, +0.04).

Subgroup analyses: data available for analysis by birth weight (see section 01.67) and by route of administration, by total dose, serum level, onset and duration of therapy in the treatment group. Vitamin E supplementation did not significantly affect this outcome in any of the analyses.

**Reaction at the site of injection in very low birth weight infants (Outcome 01.68):**

This outcome was assessed in a single study involving 73 treated patients and 74 controls. Vitamin E supplementation did not significantly affect the risk of reaction, estimate RR 5.07, CI 0.25, 103.78; RD 0.03, CI -0.02, +0.074.

**VITAMIN E VERSUS ANOTHER TYPE OR ROUTE OF VITAMIN E FORMULATION (COMPARISON 02):**

Only one study was found in this category. Bonati 1991 did not show any significant difference in mortality (Outcome 02.01) and did not assess the other planned primary outcomes (long-term combined outcomes). This study did not show any significant difference in any of the analyzed secondary outcomes, including bronchopulmonary dysplasia (Outcome 02.02), patent ductus arteriosus (Outcome 02.03), sepsis (Outcome 02.04), intracranial hemorrhage (Outcome 02.05), parenchymal hemorrhage (Outcome 02.06), necrotizing enterocolitis (Outcome 02.07), or exchange transfusion (Outcome 02.08). Plasma levels of free tocopherol peaked on day three, after three injections of vitamin E. In the treatment group, plasma levels of tocopheryl acetate were one third of levels of free tocopherol. In the control group receiving tocopherol in olive oil, plasma levels of free tocopherol were within deficient range and significantly lower than those receiving the colloidal solution of tocopheryl acetate.

## DISCUSSION

### SUMMARY OF THE RESULTS :

#### VITAMIN E VERSUS PLACEBO OR NO VITAMIN E (COMPARISON 01):

##### Primary outcomes:

Vitamin E supplementation did not significantly affect mortality in all patients and in very low birth weight infants; the strength of this inference is strong, based on more than 1500 randomized patients and no evidence of heterogeneity. No study assessed combined outcomes at 18 months of age.

##### Secondary outcomes:

##### *Bronchopulmonary dysplasia :*

Vitamin E supplementation did not significantly affect these outcomes (except for some subgroup analyses of patent ductus arte-

rius requiring treatment). The strength of these inferences is strong, based on 500-900 randomized patients and no evidence of heterogeneity.

#### ***Patent ductus arteriosus:***

Vitamin E supplementation did not significantly affect patent ductus arteriosus. The strength of this inference is strong, based on 500-900 randomized patients and no evidence of heterogeneity. However, there was significant heterogeneity for patent ductus arteriosus requiring treatment, and some subgroup analyses reached statistical significance.

#### ***Sepsis:***

Vitamin E supplementation significantly increased the risk of sepsis after study entry among all infants (typical estimate RR 1.52, CI 1.13, 2.04). The strength of this inference appears strong, based on a large number of randomized patients (>1000) and no evidence of heterogeneity. However, there is heterogeneity in RD. Vitamin E supplementation significantly increased the risk of sepsis after study entry among very low birth weight infants (typical estimate RR 1.53, CI 1.13, 2.08), and among very low birth weight infants treated for more than one week (typical estimate RR 1.63, CI 1.17, 2.26). The strength of this inference is strong, based on 500-900 randomized patients and no evidence of heterogeneity. Subgroup analysis showed that this effect was associated with parenteral vitamin E supplementation, intravenous supplementation, at dose greater than 30 IU/kg/day, starting within 48 hours after life, with serum tocopherol levels greater than 3.5 mg/dl, and with vitamin E intake in the control group that was equal to or lower than 10 mg/100 kcal. In contrast, vitamin E did not significantly affect the risk of sepsis among surviving very low birth weight infants (n=274).

#### ***Intracranial hemorrhage:***

Vitamin E supplementation significantly reduced the risk for germinal matrix/intraventricular hemorrhage among all infants (n=1755) (typical estimate RR 0.85, CI 0.73, 0.99). The strength of this inference appears strong, based on a large number of randomized patients and no evidence of heterogeneity. However, there is heterogeneity in RD. Subgroup analyses suggest that this heterogeneity may be related in large part to differences in route of administration; specifically, subgroup analyses of intravenous versus other routes of administration completely eliminated this heterogeneity. Intravenous vitamin E supplementation did not significantly affect the risk of hemorrhage (01.19.05), whereas administration by other than the intravenous route (01.19.06) significantly reduced that risk (typical estimate RR 0.71, CI 0.58, 0.87; RD -0.14, CI -0.22, -0.06).

Among very low birth weight infants, vitamin E supplementation did not significantly affect the risk for germinal matrix/intraventricular hemorrhage; although the strength of this inference

appears strong, based on a large number (n=777) of randomized patients and no statistical evidence of heterogeneity, a word of caution is required. Subgroup analysis excluding high-dose intravenous vitamin E only counted a single study (Fish 1990) involving only 147 patients and yielding an estimate RR of 0.70, CI 0.46, 1.04, which is in the same range as that cited above in this paragraph for all premature infants.

The effect of vitamin E supplementation on severe intraventricular hemorrhage or on parenchymal hemorrhage was heterogeneous. Vitamin E supplementation did not significantly affect the risk of severe intraventricular hemorrhage or parenchymal hemorrhage among all infants or among very low birth weight infants. In extremely low birth weight infants vitamin E supplementation did not significantly affect the risk for severe hemorrhage (n=232) in studies analyzing the data on intention to treat basis, but significantly reduced the risk of severe intraventricular hemorrhage in survivors (n=133). This discrepancy resulted from the fact that vitamin E reduced the risk of severe hemorrhage only in survivors in Fish 1990. The effects of vitamin E on parenchymal hemorrhage could have resulted from several differences in design between two studies: intravenous high-dose, prolonged administration of vitamin E including in extremely low birth weight infants was associated with an increased risk in one study, whereas intramuscular, low-dose, short administration was associated with a reduced risk in another study.

#### ***Retinopathy of prematurity:***

Vitamin E supplementation did not significantly affect the risk of retinopathy of prematurity (all grades) among all infants (typical estimate RR close to 1 in all analyses). The strength of this inference is strong, based on more than 1300 randomized patients and no evidence of heterogeneity.

Vitamin E supplementation did not significantly affect the risk of severe retinopathy of prematurity among all infants (typical estimate RR 0.72, CI 0.41, 1.25) and among very low birth weight infants (typical estimate RR 0.59, CI 0.32, 1.08) in an intention to treat analysis. The strength of this inference appears strong, based on more than 1300 randomized patients and no statistical evidence of heterogeneity. Nevertheless, the RR is not close to 1 in either of these analyses. Among examined very low birth weight infants, vitamin E significantly reduced the risk for severe retinopathy of prematurity (n=1062) (typical estimate RR 0.58, CI 0.34, 1.00) and the risk for blindness (typical estimate RR 0.19, CI 0.10, 0.88, n=467) but not retinal detachment (too rare to reach any solid conclusion) nor the risk for reaching a final cicatricial stage. The reduction in risk for severe retinopathy was observed with serum levels greater than 3.5 mg/dl (typical estimate RR 0.34, CI 0.13, 0.88 for all infants and 0.34, CI 0.13, 0.87 for very low birth weight infants), but not with lower levels (typical estimates RR 0.83, CI 0.42, 1.61 and 1.01, CI 0.44, 2.32, respectively). Reduced risk of blindness was observed in very low-birth weight infants receiving



vitamin E starting within 48 hours of life and for more than a week.

Our results on retinopathy of prematurity are similar although not identical to those of a recent systematic review (Raju 1997), which analyzed retinopathy of prematurity after reclassifying individual outcomes according to the International Classification for Retinopathy of Prematurity. The odds ratio for retinopathy of prematurity among very low birth weight infants using an intention-to-treat analysis was 0.85 (CI 0.65, 1.11) in Raju 1997, compared with 0.83 (CI 0.62, 1.11) in our study. The odds ratio using an intention-to-treat analysis was 0.44 (CI 0.21, 0.87) for severe retinopathy (ROP 3+) in Raju 1997, compared with 0.57 (CI 0.30, 1.09) for ROP  $\geq 3$  in our study; analysis among patients examined reached significance in Raju 1997 as well as in our analysis.

#### ***Necrotizing enterocolitis:***

Vitamin E supplementation did not significantly affect the risk of necrotizing enterocolitis among all infants and among very low birth weight infants (typical estimate RR 1.37, CI 0.93, 1.95). The strength of this inference appears strong, based on more than 1340 randomized patients and no statistical evidence of heterogeneity. Nevertheless, the typical estimate RR is not close to 1 and RR in individual studies varies between 0.51 and 6.88.

Among 734 very low birth weight infants treated for more than one week, the typical estimate RR was 1.51 (CI 0.99, 2.30), reaching significance in infants with birth weight less than 1500 grams and in those with serum tocopherol levels greater than 3.5 mg/dl. The strength of this inference is limited by lack of intention-to-treat analysis and by heavy weighing of the results towards a single study using high-dose intravenous vitamin E administration (Johnson 1989).

#### ***Hematologic outcomes:***

Vitamin E supplementation significantly increased hemoglobin by a small amount (0.4 g/dl) in more than 400 patients and without evidence of heterogeneity, and significantly reduced reticulocyte count. Nevertheless, it did not affect the need for transfusion. In very low birth weight infants, vitamin E significantly reduced serum bilirubin by 1.5 mg/dl.

Low-dose, enteral administration of vitamin E did not significantly affect platelet counts or coagulation tests.

High-dose intravenous administration of vitamin E significantly increased the risk of retinal hemorrhage among 85 extremely low birth weight infants in a single study (Phelps 1987a) but not among the whole set of 232 very low birth weight infants. This is the same study in which vitamin E significantly increased the risk of parenchymal intracranial hemorrhage (01.28). Rosenbaum had found a statistical association between severe intraventricular hemorrhage and later retinal hemorrhage ( $p < 0.007$ , Fisher's exact test (Phelps 1987a). Mean peak tocopherol levels were 5.07+/-

-3.41 mg/dl in patients with retinal hemorrhage versus 3.49+/-3.22 mg/dl in those without retinal hemorrhage ( $p = 0.025$ ).

#### **Summary:**

Summary statistics using intention-to-treat analyses showed that routine vitamin E supplementation significantly reduced the risk of germinal/intraventricular hemorrhage (RR 0.85, CI 0.73, 0.99) and increased the risk of sepsis after study entry (RR 1.52, CI 1.13, 2.04) but did not significantly affect mortality, bronchopulmonary dysplasia, patent ductus arteriosus, severe intraventricular hemorrhage, parenchymal hemorrhage, retinopathy of prematurity, platelet count, or coagulation studies. Hemoglobin concentration was significantly increased by a small amount (WMD 0.46, CI 0.24, 0.69). In very low birth weight infants, vitamin E supplementation significantly increased the risk for sepsis after study entry (RR 1.53, CI 1.13, 2.08) and, although with significant heterogeneity, the risk for parenchymal hemorrhage (RR 9.21, CI 1.22, 69.58); among those with known outcomes vitamin E significantly reduced the risk for severe retinopathy (RR 0.58, CI 0.34, 1.00) and blindness (RR 0.29, CI 0.10, 0.88).

Subgroup analyses showed that (1) serum tocopherol levels greater than 3.5 mg/dl in very low birth weight infants were associated with a significantly increased risk of sepsis after study entry (RR 1.72, CI 1.24, 2.40), with increased risk of necrotizing enterocolitis among those treated for more than one week (RR 1.60, CI 1.02, 2.52) and with reduced risk for severe retinopathy among those examined (RR 0.34, CI 0.13, 0.88); and (2) intravenous, high-dose administration of vitamin E in very low birth weight infants was associated with a significantly increased risk of sepsis after study entry (RR 1.56, CI 1.07, 2.27), with increased risk of parenchymal hemorrhage in one study only and with increased risk of necrotizing enterocolitis among those treated for more than one week in another study.

#### **Colloidal vitamin E versus vitamin E in olive oil:**

Colloidal vitamin E resulted in higher serum levels, but did not significantly affect any of the analyzed outcomes.

#### **Discussion:**

In this systematic review, a large number of subgroup analyses was undertaken. This must lead to caution in inferring the likely effects of treatment when estimated in multiple subgroups.

Although this systematic review shows that high-dose intravenous vitamin E has toxic effects, these data should not be taken as evidence that intravenous vitamin E at any dose is toxic. Based on all the available evidence from this systematic review and from data presented in the background, the dose recommended by the American Society for Clinical Nutrition (2.8-3.5 IU/kg/day) (Greene 1988) for extremely low birth weight infants should remain the current standard of care for those fed parenterally.



The majority of the clinical trials available in this systematic review were conducted in the 1980s or earlier, so that too few surviving extremely preterm infants were available to permit subgroup analysis of this most vulnerable population. Thus, recommendations based on the available subjects must be viewed with caution when applied to the group of preterm infants inhabiting the modern neonatal unit. The current population includes many infants who are more premature and smaller than the infants on whom the recommendations were based. Furthermore, the only major long-term benefit of vitamin E supplementation demonstrated in this review was the prevention of blindness in very low birth weight infants, the incidence of which has been substantially reduced with laser photo coagulation.

Because the majority of clinical trials available for this review analyzed infants who currently are not the ones at high risk for threshold retinopathy of prematurity, and because severe retinopathy is relatively frequent in extremely low birth weight infants, it would appear justified to initiate a multicenter randomized trial assessing the effects in this population of supplementation with vitamin E (excluding high-dose intravenous administration) begun within 48 hours of birth and given for more than one week. Only three studies provided extremely low birth weight infants meeting these criteria and available for analysis in this systematic review: [Ehrenkranz 1982](#); [Fish 1990](#); [Hittner 1981](#), in which mean serum tocopherol levels in the treatment group were, respectively, 3.89, 4.24 and 1.21 mg/dl. In the latter study, serum levels in control patients were compatible with vitamin E deficiency. Thus, only the first two studies should be used as baseline. The numbers of patients available to our analysis were 147 for mortality (01.02.03), sepsis (01.16.03), germinal matrix/intraventricular hemorrhage (01.20.03), severe intraventricular hemorrhage (grade III/IV) (01.25.02) and necrotizing enterocolitis (01.45.03), nine for retinopathy of prematurity among patients examined (01.34.03) and for severe retinopathy (grade 3 or more) (01.36.03) and blindness (01.43.03), and none for retinopathy of prematurity (any grade) (01.32.03), parenchymal hemorrhage (grade IV) (01.28), retinal detachment among survivors (01.40.03) and retinal bleeding (01.66.02). Among patients examined, the typical estimate RR was 1.67 for sepsis (01.16.03), 0.70 for germinal matrix/intraventricular hemorrhage (01.20.03), 0.59 for severe intraventricular hemorrhage (01.25.02), 0.27 for retinopathy of prematurity among patients examined (01.34), 0.12 for severe retinopathy of prematurity (01.38.03), not estimable for blindness (01.43.03), and 0.51 for necrotizing enterocolitis (01.45.03). Thus, preliminary analysis suggests that potential benefits might include a reduction of severe intraventricular hemorrhage and retinopathy and potential toxicity might include sepsis.

## AUTHORS' CONCLUSIONS

### Implications for practice

Available data show that vitamin E supplementation in very low birth weight infants reduces severe retinopathy at high serum tocopherol levels, i.e., those associated with sepsis. Doses of vitamin E greater than 30 IU/kg/day are also associated with sepsis. Thus, the "best" pharmacologic dose of vitamin E is unclear at this point. Evidence argues against the use of intravenous vitamin E supplementation, high doses or routes yielding serum tocopherol levels greater than 3.5 mg/dl in preterm infants including very low birth weight infants.

### Implications for research

It would appear justified to initiate in extremely low birth weight infants a multicenter randomized trial assessing the effects of supplementation with vitamin E (excluding high-dose intravenous administration) begun within 48 hours of birth and given for more than one week. Such a study should examine the incidence of severe retinopathy of prematurity, blindness, severe intracranial hemorrhage, sepsis, and long-term neurodevelopmental outcome. The study should focus on the most immature infants (less than 28 weeks gestational age and less than 1000 grams birth weight) because these infants are at the highest risk of complications of prematurity. If a new multicenter trial is to be undertaken, it should be designed to allow careful monitoring for toxicity, and, if doses greater than 30 IU/kg/day are to be tested, serum tocopherol levels should be monitored. It is unclear whether target levels should be below or above 3.5 mg/dl because high levels were those associated both with increased risk of sepsis and with reduced risk for severe retinopathy. Furthermore, such trial may be more controversial than other interventions which may reduce the risk of severe retinopathy of prematurity without apparent severe side effects, e.g., reducing oxygen administration and allowing a decrease in oxygen saturation ([Tin 2001](#); [Chow 2003](#)).

## ACKNOWLEDGEMENTS

We wish to thank Ms. Diane Haughton and Dr. Bosco Paes for providing us with a copy of Milner's 1981 manuscript ([Zipursky 1987](#)). We thank Ms. Melody Thompson, MS, RD, Ms. Mary L Banish and Mr. Jason Miller from Ross Products Division of Abbott Laboratories, who searched for additional references for this review. We thank Philip Roth, MD, PhD, for allowing us to present a study in press ([Pathak 2003](#)).

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\* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

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

#### Bonati 1991

Methods	Design: multi-center randomized trial. Method of randomization: random allocation of the first baby; alternating medication in subsequent infants. Blinding of intervention: no. Complete follow-up: no; data reported on the 44 infants who completed the 3-day schedule of vitamin E. Blinding of outcome: no.
Participants	Total number of patients entered into the study: 50. Data reported in 22 patients in each group. Entry criteria: liveborn, gestational age equal or less than 32 weeks, no malformations, born in participating centers over 3 months, admitted to a neonatal intensive care within 2 hours of birth
Interventions	Treatment: 20 mg/kg dl-alpha-tocopheryl acetate given intramuscularly as aqueous colloidal solution (Ephynal, Hoffmann-La Roche, Basel, Switzerland). Control: 20 mg/kg vitamin E given intramuscularly as alpha-tocopherol in an olive solution (Evion Forte, Bracco, Milano) on three consecutive days, starting within 8 hours of life.
Outcomes	Mortality, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, patent ductus arteriosus, phototherapy, exchange transfusion
Notes	Plasma tocopherol level: treatment group: $3.60 \pm 1.12$ mg/dl; control group: $0.31 \pm 0.20$ mg/dl

#### *Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

#### Chiswick 1982

Methods	Design: Randomized trial. Method of randomization: not described. Blinding of intervention: no. Complete follow-up: yes. Blinding of outcome: no.
Participants	Total number of patients entered into the study: 35. Treatment group: 14; control group: 21. Entry criteria: preterm infants without major congenital malformations
Interventions	Treatment: dl-alpha-tocopheryl acetate (Ephynal, Hoffmann-La Roche) 20 mg/kg given intramuscularly daily for 4 doses commencing within 24 hours after birth. Control: no injection
Outcomes	Mortality, intraventricular hemorrhage
Notes	Plasma tocopherol level: treatment group $4.84 \pm 2.37$ mg/dl; control group $0.58 \pm 0.29$ mg/dl

#### *Risk of bias*

**Chiswick 1982** (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Chiswick 1983**

Methods	Design: Randomized trial. Method of randomization: not provided. Blinding of intervention: not mentioned. Complete follow-up: yes. Blinding of outcome: not mentioned.
Participants	Total number of patients entered into the study: 44. Treatment group: n=21, control group: n=23. Entry criteria: gestational age less than 37 weeks and birth weight less than 1751 g.
Interventions	Treatment: dl-alpha-tocopheryl acetate (Ephynal, Hoffmann-La Roche) 20 mg/kg given intramuscularly at 12, 36 and 60 hours of life. Control: no injection
Outcomes	Mortality, germinal matrix/intraventricular hemorrhage, intraventricular hemorrhage
Notes	Plasma tocopherol level: treatment group 3.69±1.41 mg/dl; control group 0.42±0.38 mg/dl

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Cruz 1983**

Methods	Design: Randomized trial (groups I and II). Method of randomization: not provided. Blinding of intervention: no, Complete follow-up: yes. Blinding of outcome: no.
Participants	Total number of patients entered into the study: 53 mothers and 55 infants. Groups I and II: 27 and 28, respectively (randomized); group III: 40 (not randomized). Entry criteria: (1) mothers admitted with threatened premature delivery at 26-34 weeks of gestation, (2) infant's birth weight less than 2,300 g
Interventions	Group I: mother given vitamin E orally 900 mg for three days, followed by 100 mg daily until delivery. Infant given intramuscular vitamin E 25 mg/kg on days 1,2,4 and 8. Group II: mother given vitamin E orally as in group I, infant given no vitamin E injection. Group III (not randomized): neither mother nor infant received vitamin E supplementation.
Outcomes	Retrolental fibroplasia, bronchopulmonary dysplasia
Notes	Oral multivitamin drops started on day five of life, this provided two mg of vitamin E daily. Plasma tocopherol level on day 9: treatment group 4.14±1.08 mg/dl, control group 0.91±0.46 mg/dl

**Cruz 1983** (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Ehrenkranz 1982**

Methods	Design: randomized double-blind trial. Method of randomization: not provided. Blinding of intervention: yes. Complete follow-up: yes, except for intraventricular hemorrhage. Blinding of outcome: yes.
Participants	Total number of patients entered into the study: 100. Treatment group: 47, control group: 53. Entry criteria: respiratory distress syndrome, informed consent.
Interventions	Treatment: 20 mg/kg vitamin E Injectable (Hoffmann-LaRoche) intramuscularly upon admission to the study (first day of life) and 24, 48, and 168 hours later, and then twice weekly as long as the infant remained in oxygen and could not tolerate feedings and vitamin supplements. Control: placebo.
Outcomes	Mortality, bronchopulmonary dysplasia, patent ductus arteriosus, patent ductus arteriosus requiring therapy, intraventricular hemorrhage, retrolental fibroplasia
Notes	All infants received initially an intravenous protein solution containing vitamin E 2.5 U/L. Enteral feeding provided 16 U/L (formula) or 3 U/L (human milk). Patients tolerating feeds regularly were given oral vitamin E supplementation (Aquasol E, USV Pharmaceutical Corp.) at a dose of 50 IU/day if weight was < 1000 g and 25 IU/day if weight was > 1000 g. Plasma tocopherol level: treatment group 3.89±1.31 mg/dl, control group 0.78±0.37 mg/dl

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Ferlin 1998**

Methods	Design: randomized trial. Method of randomization: not provided. Blinding of intervention: yes. Complete follow-up: unclear (by design, only patients with regular follow-up visits were included). Blinding of outcome: yes.
Participants	Total number of patients entered into the study: 40. Group I: 10, II: 10; III: 10; IV: 10. Entry criteria: birth weight less than or equal to 1600 g and gestational age less than or equal to 35 weeks, informed consent, stable clinical course, no blood transfusion, regular follow-up visits after discharge, absence of interfering events that would require discontinuation of medications.

**Ferlin 1998** (Continued)

Interventions	Four groups: I: placebo started on the 15th day of life, iron starting at 2 months of age; II: 4 mg/kg/day iron started on the 15th day of life; III: 4 mg/kg/day iron and 25 IU/day alpha-tocopherol (Roche) orally started on the 15th day of life; IV: 25 IU/day vitamin E started on the 15th day of life.	
Outcomes	Hemoglobin	
Notes	All infants received 1.5 IU vitamin E/day and 0.1 mg iron (in multivitamin preparation)starting on the 7th day of life. Iron supplementation started at 2 months of age in patients who not yet supplemented.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Finer 1982**

Methods	Design: randomized trial. Method of randomization: sealed envelopes, stratification by birth weight and by severity of respiratory distress (requirement for oxygen and endotracheal intubation). Blinding of intervention: no. Complete follow-up: no. Most data are available only for the 99 infants who completed the trial. Blinding of outcome: yes.	
Participants	Total number of patients entered into the study: 126. Treatment group: 62, control group: 64. Entry criteria: birth weight between 750 and 1500 g, appropriate for gestational age, informed consent.	
Interventions	Treatment: 25 mg vitamin E, two doses, administered intramuscularly respectively within 12 hours of birth and 12 hours afterwards; then 20 mg intramuscularly daily for 14 days, then 20 mg intramuscularly every 3 days for 5 doses; then either 100 U daily orally or (if feeds not tolerated)20 mg intramuscularly every 3 days. Control: no vitamin E.	
Outcomes	Bronchopulmonary dysplasia, patent ductus arteriosus, retrolental fibroplasia among infants survived/ examined, blindness from retrolental fibroplasia, necrotizing enterocolitis	
Notes	Osmolality of the oral preparation, used as a 1:1 dilution: 2,025 mOsm/kg. Plasma tocopherol level: treatment group 4.21±3.35 mg/dl, control group 0.71±0.67 mg/dl. Outcome variables available among infants surviving/examined: retrolental fibroplasia, blindness from retrolental fibroplasia	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Fischer 1987**

Methods	Design: randomized double-blind trial. Method of randomization: not provided. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome: yes.	
Participants	Total number of patients entered into the study: 28. Treatment group: 17, control group: 11. Entry criteria: birth weight less than 1,500 g, normal size for gestational age, informed consent . entered during the first 24 hours of life	
Interventions	Treatment: oral administration of d-alpha-tocopherol polyethylene glycol-1000-succinate, 50 mg/day for three doses. Control: placebo.	
Outcomes	Bilirubin, hemoglobin	
Notes	Several infants randomized to treatment group received only 25 mg/day. Plasma tocopherol level: treatment group 1.85±0.76 mg/dl, control group 0.76±0.49 mg/dl	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Fish 1990**

Methods	Design: randomized double-blind trial. Method of randomization: by the pharmacy, stratified by birth weight. Blinding of intervention: no. Complete follow-up: no: two infants were excluded because of initially inapparent structural anomalies. Blinding of outcome: yes.	
Participants	Total number of patients entered into the study: 149, of which two were excluded after entry. Treatment group: 73, control group: 74. Entry criteria: birth weight equal to or less than 1000 g, postnatal age equal to or less than 24 hours, informed consent. Exclusion criteria: extremely poor condition on admission, major congenital abnormalities.	
Interventions	Treatment: dl-alpha-tocopherol (Ephynal, Hoffmann-La Roche) intramuscularly in four doses at 15,10,10 and 10 mg/kg on days 1,2,4, and 6 of life, respectively. Doses of dl-alpha-tocopherol 10 mg/kg were administered intramuscularly every 3 days if the attending neonatologist felt that the infant could not tolerate oral vitamin E (see Notes) after 7 days of life. Control: placebo.	
Outcomes	Mortality, intracranial hemorrhage, necrotizing enterocolitis, sepsis, patent ductus arteriosus, local reaction at injection site	
Notes	Plasma tocopherol levels were not blinded to the clinicians. All neonates received oral dl-alpha-tocopheryl acetate (Aquasol E) 100 mg/kg/day beginning at admission; dose adjusted after day 7 to maintain total vitamin E serum level 0.5-3.5 mg/dl. Plasma tocopherol level during first week: treatment group 4.24±1.59 mg/dl, control 1.95±1.04 mg/dl; after first week: treatment group 2.70±0.09 mg/dl, control group 2.39±0.09 mg/dl	

**Fish 1990** (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Graeber 1977**

Methods	Design: randomized trial. Method of randomization: not provided. Blinding of intervention: no. Complete follow-up: yes. Blinding of outcome: no.
Participants	Total number of patients entered into the study: 35. Groups I: 5, II: 5, III: 5, IV: 5, V: 5, VI: 10. Entry criteria: birth weight less than 1,500 g, gestational age less than 34 weeks. Exclusion criteria: ABO or Rh isoimmunization, hemoglobin value less than 13 g/dl at seven days of age, transfusion of whole blood or plasma at any age, transfusion of red blood cells after one week of age.
Interventions	Treatment: (1) intramuscular dl-alpha-tocopheryl acetate in a water-dispersible vehicle (Roche) with total dose divided in four aliquots (days 1,2,7 and 8); (2) Intramuscular iron: iron-dextran complex (Imferon): 25 mg/day on days 7,14,21, and 28; control: no injection. Control: no injection. Six groups (by dose of vitamin E and dose of iron) in the original trial: Group I: total dose of vitamin E: 100 mg/kg, no iron; group II: vitamin E 125 mg/kg, no iron; group III: vitamin E 150 mg/kg, no iron; group IV: vitamin E 125 mg/kg and iron 100 mg; group V: no vitamin E, iron 100 mg; group VI: neither vitamin E, nor iron.
Outcomes	Bronchopulmonary dysplasia, retrolental fibroplasia
Notes	Plasma tocopherol level: treatment group 1.78±0.60 mg/dl, control group 0.53±0.34 mg/dl

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Gross 1977**

Methods	Design: randomized trial. Method of randomization: not provided. Blinding of intervention: no. Complete follow-up: yes. Blinding of outcome: no.
Participants	Total number of patients entered into the study: 20. Treatment group: 10, control group: 10. Entry criteria: birth weight less than 2,500 g, gestational age less than 36 weeks, well, breathing room air, hemoglobin concentration greater than 13 g/dl on the third day of life. Exclusion criterion: Rh or ABO isoimmunization.
Interventions	Treatment: total dose of 125 mg/kg tocopheryl acetate (Roche) administered intramuscularly in 8 divided doses, an injection in each thigh, on days 4,5,6 and 7 of life. Control: no injection.

**Gross 1977** (Continued)

Outcomes	Hemoglobin	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Gross 1979**

Methods	Design: randomized trial. Method of randomization: not provided. Randomization stratified by weight (1000-1500 g and 1501-2000 g). Blinding of intervention: no. Complete follow-up: yes. Blinding of outcome: no.	
Participants	Total number of patients entered into the study: 40; treatment group: 20, control group: 20. Entry criteria: birth weight between 1000 and 2000 g, appropriate for gestational age. Exclusion criteria: hemoglobin concentration less than 13 g/dl, Rh or ABO isoimmunization.	
Interventions	Treatment: total dose of 50 mg/kg dl-alpha-tocopheryl acetate (Roche) administered intramuscularly in 6 divided doses, an injection in each thigh on days 1,2, and 3 of life. Control: no injection.	
Outcomes	Serum bilirubin	
Notes	Plasma tocopherol level: treatment group 3.00±1.00 mg/dl, control group 0.50±0.30 mg/dl	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Hittner 1981**

Methods	Design: randomized double-blind trial. Method of randomization: random-number table. Randomization stratified by weight. Blinding of intervention: yes. Complete follow-up: no: information on 49 patients is incomplete. Blinding of outcome: yes.	
Participants	Total number of patients entered into the study: 150. One patient with necrotizing enterocolitis was excluded (no information on treatment allocation). Treatment group: 75, control group: 74. Entry criteria: birth weight less than or equal to 1,500 g, requiring oxygen for respiratory distress, admitted to the unit within the first 24 hours of life, informed consent. Exclusion criteria: necrotizing enterocolitis preventing oral administration of vitamin E (n=1); exclusion from all other outcomes: death before four weeks (n=48).	



## Hittner 1981 (Continued)

Interventions	Treatment: dl alpha-tocopherol 100 mg/kg/day orally, provided as water-dispersible liquid containing dl alpha-tocopherol 50 mg/ml in propylene glycol-polysorbate 80. Control (placebo): dl alpha-tocopherol 5 mg/kg/day orally, provided as 2.5 mg/ml in propylene glycol-polysorbate 80. Treatment and placebo were started on the first 24 hours of life and continued throughout the hospital stay.	
Outcomes	Mortality. Outcomes among patients surviving four weeks: bronchopulmonary dysplasia, patent ductus arteriosus, sepsis, periventricular- intraventricular hemorrhage, retrolental fibroplasia	
Notes	Osmolality of the oral preparation: 3000 mOsm/kg. Plasma tocopherol level: treatment group 1.21±0.79 mg/dl, control group 0.62±0.40 mg/dl. Outcome variables available only among patients surviving at least four weeks and without necrotizing enterocolitis: bronchopulmonary dysplasia, patent ductus arteriosus, sepsis, periventricular-intraventricular hemorrhage and retrolental fibroplasia.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

## Hittner 1984

Methods	Design: double-masked randomized trial. Method of randomization: random-number table. Randomization stratified by weight. Blinding of intervention: yes. Complete follow-up: no: information incomplete in 33 infants not surviving ten weeks (primary reference) or in 34 outpatients (secondary reference). Blinding of outcome: yes.	
Participants	Total number of patients entered into the study: 168. Treatment group: 79, control group: 89. Entry criteria: birth weight equal to or less than 1,500 g, oxygen requirement for respiratory distress, admission within 24 hours, informed consent. Exclusion criteria from all other outcomes: death before 10 weeks (n=33).	
Interventions	Treatment: dl-alpha-tocopherol, 55 mg/ml (Ephynal, Hoffman-La Roche, preparation containing benzyl alcohol, propylene glycol, ethyl alcohol, Emulphor E1-620, and buffering salts), given intramuscularly at doses of 15, 10, 10, and 10 mg/kg on days 1,2,4 and 6 of life. Control: placebo injections.	
Outcomes	Mortality. Outcomes available either among patients surviving ten weeks or among inpatients: bronchopulmonary dysplasia, patent ductus arteriosus, sepsis, periventricular-intraventricular hemorrhage, retrolental fibroplasia, necrotizing enterocolitis, number of transfusions and amount of blood transfused	
Notes	Vitamin E 100 mg/kg/day given orally to all infants starting within the first 24 hours of life. This was provided as an emulsion of dl-alpha-tocopheryl acetate in gelatin, silicon dioxide, polysorbate 80, and medium chain triglycerides, osmolality 150 mOsm/kg. Plasma tocopherol level: treatment group 3.29±1.58 mg/dl, control group 1.42±1.12 mg/dl. Outcome variables available among those surviving ten weeks: bronchopulmonary dysplasia, patent ductus arteriosus, sepsis, periventricular-intraventricular hemorrhage, retrolental fibroplasia, necrotizing en-	

**Hittner 1984** (Continued)

	terocolitis, number of transfusions and amount of blood transfused	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Jansson 1978**

Methods	Design: randomized trial. Method of randomization: not provided. Randomization stratified by weight (1000-1999 and 2000-2499 g). Blinding of intervention: no. Complete follow-up: yes. Blinding of outcome: no.	
Participants	Total number of patients entered into the study: 57. Group I: 24, group II: 17, group III: 16. Entry criteria: birth weight less than 2500 g. Exclusion criteria: hemoglobin concentration below 15 g/dl or greater than 26 g/dl in the first 24 hours, hyperbilirubinemia, blood transfusion.	
Interventions	Group I (control): ferrous succinate starting at 3 weeks of age (elemental iron 2-3 mg/kg/day); group II: dl-alpha-tocopheryl acetate (E-vitamin, AB ACO, dispersible in lipid solutions) 15 mg/day started at 10 days and ferrous succinate started at 3 weeks; group III: tocopheryl acetate 15 mg/day started at 10 days and ferrous succinate started at 10 weeks.	
Outcomes	Hemoglobin, reticulocyte count, platelet count	
Notes	From 10 days of age, all infants received 1.5 mg/day of tocopheryl acetate orally. Plasma tocopherol level: treatment group 1.22±0.20 mg/dl, control group 0.80±0.28 mg/dl	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Johnson 1989**

Methods	Design: randomized, double-blind controlled trial. Method of randomization: not provided. Randomization stratified by hospital and by birth weight. Blinding of intervention: yes. Complete follow-up: no; complete data available in only 755 of 914 enrolled. Blinding of outcome: yes.	
Participants	Total number of patients entered into the study: 914. Treatment group: 454, control group: 460. Entry criteria: (1) birth weight equal to or less than 2000 g or (2) gestational age equal to or less than 36 weeks and oxygen treatment required; informed consent, admission within 5 days of age. Sixty-eight percent of the infants were enrolled by calendar age one day.	
Interventions	Treatment: (1) infants receiving intravenous feeding: 15 mg/kg vitamin E intramuscularly and 15 mg/kg intravenously at study admission, followed by 15 mg/kg intravenously the next day; (2) infants receiving	

**Johnson 1989** (Continued)

	oral feedings: 15 mg/kg vitamin E intramuscularly and 100 mg/kg/day divided in aliquots in the feeds. Subsequent dosage adjusted to maintain serum vitamin E level of 5 mg/dl. Control: placebo both for oral and parenteral preparations, with dosage adjustments to mimic those in the control group. Study medication was replaced by vitamin E in patients who had developed severe ROP.	
Outcomes	Retinopathy of prematurity and serum bilirubin. Among infants with birth weight less than or equal to 1500 g: mortality, bronchopulmonary dysplasia (diagnosed radiographically), sepsis, intraventricular hemorrhage, retinopathy of prematurity, and necrotizing enterocolitis	
Notes	<p>Vitamin E was provided as free dl-alpha-tocopherol 50 mg/ml (55 IU/ml) emulsified for parenteral administration with Emulfor 620. This is one of the two studies in which vitamin E was administered intravenously.</p> <p>Plasma tocopherol level: treatment group 5.10±1.90 mg/dl, control group 0.82±0.36 mg/dl.</p> <p>Examination for the presence of retinopathy of prematurity was done in 755 patients. Outcome variables available among the 545 infants with birth weight less than or equal to 1500 g: mortality, bronchopulmonary dysplasia (diagnosed radiographically), patent ductus arteriosus, patent ductus arteriosus requiring treatment, sepsis after study entry, intraventricular hemorrhage, retinopathy of prematurity, and necrotizing enterocolitis. Outcome variables available in subsets of the population included sepsis after study entry among very low birth weight infants treated for more than one week, bilirubin (excluding hemolytic anemia, polycythemia, and prior transfusion, and amount of blood transfusion (subset of very low birth weight infants).</p>	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Melhorn 1971**

Methods	Design: randomized controlled trial. Method of randomization: not provided. Randomization stratified by weight and gestational age. Complete follow-up: no: data are provided on only 186 patients. Blinding of outcome: no	
Participants	Total number of patients entered into the study: 234, including some full-term infants. Group I: 45, II: 47, III: 44, IV: 50. Entry criteria: admission to the premature nursery unit. Exclusion criteria: either small or large for gestational age, hemoglobin concentration < 14 g/dl in the first 24 hours of life, blood group incompatibility, hemoglobinopathy, red blood cell enzyme deficiency, infection, defects requiring surgical intervention.	
Interventions	Group I: no supplement (control). Group II: vitamin E: alpha tocopheryl acetate 25 units/day orally from the eighth to the forty-second day of life. Group III: iron from the fifteenth to forty-second day of life: 10 mg/day if weight < 1500 g, 15 mg/day if weight 1501-2000 g, 20 mg/day if weight > 2001 g. Group IV: iron and vitamin E.	
Outcomes	Hemoglobin, reticulocyte count	
Notes	Plasma tocopherol level: treatment group 0.5-1.0 mg/dl, control group 0.2-0.8 mg/dl	

**Melhorn 1971** (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Pathak 2003**

Methods	Design: randomized double-blind trial. Method of randomization: sealed envelopes in the pharmacy. Blinding of the intervention: no. Complete follow-up: yes. Blinding of outcome: yes
Participants	Total number of patients entered into the study: 30. Treatment group: 15, control group: 15. Entry criteria: gestational age less than or equal to 32 weeks, birth weight less than or equal to 1250 grams, clinically stable (less than 7.5 ml/week phlebotomy, oxygen requirement less than or equal to 35%, intermittent mandatory ventilation less than or equal to 25 breaths per minute, mean airway pressure less than or equal to 8 cm of water). Exclusion criteria: disease involving any major organ system, life-threatening congenital malformations or sepsis, isoimmunization with clinically apparent hemolytic anemia, hemolytic disorder, intraventricular hemorrhage grade III or greater.
Interventions	Treatment: vitamin E 50 IU/day enterally. Controls: placebo
Outcomes	Mortality, patent ductus arteriosus requiring treatment, sepsis, necrotizing enterocolitis, hemoglobin concentration, reticulocyte count, transfusions, total volume transfused
Notes	All infants received erythropoietin 100 units/kg/day five days a week for eight weeks or until discharge, whichever came first. Infants fed intravenously received a multivitamin preparation (MVI Pediatric) containing 1.4 mg alpha-tocopherol acetate/ml at dose of 1.5 ml/day and 3.25 ml/day to infants weighing < 1 kg and > 1 kg, respectively. All infants fed enterally at least 40 ml/kg/day received oral iron 6 mg/kg/day and 1 ml of a multivitamin preparation containing 5 U/ml vitamin E. Plasma tocopherol level: treatment group 2.86±1.26 mg/dl, control group 1.66±1.25 mg/dl

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

### Phelps 1987a

Methods	Design: randomized double-blind trial. Method of randomization: sealed envelopes stratified by study center, sex, and birth weight, opened at the pharmacy (center 1) or drug control center (center 2). Numbers balanced by groups of eight. Multiple births randomized separately so that one of each pair received placebo and one tocopherol. Blinding of intervention: yes. Follow-up was complete for several neonatal outcomes. However retinal examinations were not obtained in 55 infants, including nine infants lost to follow-up and 46 who had died. Blinding of outcome: yes.
Participants	Total number of patients entered into the study: 287. Treatment group: 140, control group: 147. Entry criteria included birth weight less than 1.5 kg or gestational age less than 33 weeks, less than 24 hours of age, free from recognized congenital anomalies of the eyes or congenital anomalies incompatible with survival, and informed consent. Exclusion criteria included major congenital anomalies and Rhesus hemolytic disease.
Interventions	Treatment: intravenous dose provided within 24 hours of birth and repeated on day 2 (and sometimes day 3): 20 mg/kg of nonesterified dl-alpha-tocopherol in alcohol or its vehicle (10% ethyl alcohol, 10% propylene glycol, 10% Emulphor, 1% benzyl alcohol, and buffering salts). Doses adjusted to achieve plasma vitamin E levels of 3-3.5 mg/dl; supplemental intramuscular injection given to infants with plasma levels lower than 2.5 mg/dl despite oral doses exceeding 200 mg/kg/day. Control: placebo.
Outcomes	Mortality, sepsis, late-onset sepsis, periventricular-intraventricular hemorrhage, necrotizing enterocolitis. Among survivors: retinopathy of prematurity, retinal hemorrhage
Notes	All infants fed intravenously received 1.2 mg/kg/day of tocopherol acetate in standard multivitamin supplements. In infants in whom severe ROP had developed, the study medication was replaced with vitamin E. Median plasma tocopherol level in the treatment group: 3-3.5 mg/dl (1-2 weeks of age); 2-2.5 mg/dl (3 weeks - second month). Outcome variable available among surviving infants: retinopathy of prematurity.

#### *Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

### Rudolph 1989

Methods	Design: randomized controlled trial. Method of randomization: not provided. Blinding of intervention: no. Complete follow-up: yes. Blinding of outcome: yes (cardiologist).
Participants	Total number of patients entered into the study: 29. Treatment group: 13, control group: 16. Entry criteria: preterm infant, birth weight 750-1500 g, intensive care.
Interventions	Treatment: dl-alpha-tocopherol (Hoffman-La Roche) intramuscularly at a dose of 25 mg/kg within 12 hours of birth. Repeated injections 24 hours later, and at 4, 5, 10, 20 and 30 days of age. Total cumulative dose: 175 mg/kg. Control: no vitamin E supplementation.
Outcomes	Mortality, patent ductus arteriosus, severe retinopathy of prematurity, necrotizing enterocolitis

**Rudolph 1989** (Continued)

Notes	All infants fed intravenously received 2.5 IU vitamin E per liter of parenteral solution. Plasma tocopherol level: treatment group 1.62±0.91 mg/dl, control group 0.41±0.21	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Rönnholm 1989**

Methods	Design: randomized controlled trial. Method of randomization: not provided. Blinding of intervention: no. Complete follow-up: no; incomplete information on three patients who died. Blinding of outcome: no.	
Participants	Total number of patients entered into the study: 54. Treatment group: 23; control group: 31. Entry criteria: birth weight less than or equal to 1520 g.	
Interventions	Treatment: intramuscular dU-rac-alpha-tocopheryl acetate 20 mg/kg/day (Ephynal, Hoffmann-La Roche) during the first three days of life. Controls: No injection.	
Outcomes	Bronchopulmonary dysplasia, intraventricular hemorrhage, retrolental fibroplasia, necrotizing enterocolitis	
Notes	<p>Patients were randomly supplemented with human milk protein, medium-chain triglycerides, both or neither. All patients received oral administration of water soluble vitamin E dl-alpha-tocopherol polyethyleneglycol 1000-succinate (part of a multivitamin preparation, Ekaviton, Orion Corp Ltd) in increasing doses of 1.6 mg/day on day 3 to 10 mg/day at age 2-12 weeks.</p> <p>Plasma tocopherol level in the treatment group: 1.50±0.21 mg/dl.</p> <p>Outcome variables among the 51 survivors: bronchopulmonary dysplasia, intraventricular hemorrhage, retrolental fibroplasia, and necrotizing enterocolitis.</p>	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Saldanha 1982**

Methods	Design: randomized controlled trial. Method of randomization: drawing of a card from a randomized deck. Blinding of intervention: no. Complete follow-up: no; incomplete data provided on babies who died before 10 days of age. Blinding of outcome: no.	
Participants	Total number of patients entered into the study: 44. Treatment group: 21, control group: 23. Entry criteria: gestational age less than 37 weeks, hyaline membrane disease, oxygen requirement at least 60% in first 24 hours or 80% thereafter, informed consent. Exclusion criteria: cyanotic heart disease, multiple	

**Saldanha 1982** (Continued)

	malformations, known infectious disease.
Interventions	Treatment: 25 mg of dl-alpha-tocopherol (Hoffman-La Roche) intramuscularly upon entry into the study and daily thereafter until vitamin E serum level rose above 2-4 mg/dl or until no longer oxygen requirement. Mean age at entry into the study 24±5 hours. Control: no injection. Mean age at entry into the study 18±3 hours
Outcomes	Outcomes among patients surviving ten days or more: bronchopulmonary dysplasia, patent ductus arteriosus
Notes	Plasma tocopherol level: treatment group 3.87±3.94 mg/dl, control group 0.94±1.06 mg/dl. Outcome variables among patients surviving ten days or more included: bronchopulmonary dysplasia and patent ductus arteriosus

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Schiller 1980**

Methods	Design: randomized controlled trial. Method of randomization: not provided. Blinding of intervention: no. Complete follow-up: unclear. Blinding of outcome: yes.
Participants	Total number of patients entered into the study: 29. Treatment group: 16, control group: 13. Entry criteria: preterm infant, birth weight < 1750 g.
Interventions	Treatment: dl-alpha-tocopherol intramuscularly (175 mg/kg over a 30-day period). Control: no injection.
Outcomes	Patent ductus arteriosus
Notes	Abstract only. Plasma tocopherol level: treatment group 1.70±1.22 mg/dl, control group 0.50±0.57 mg/dl

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear



**Sinha 1987**

Methods	Design: Randomized trial. Method of randomization: sealed envelope. Blinding of intervention: no. Complete follow-up: no; three infants with lethal major malformations were excluded and only partial information is provided in eighteen patients with periventricular-intraventricular hemorrhage at entry. Blinding of outcome: unclear
Participants	Total number of patients entered into the study: 231. No data are provided among three infants with lethal congenital malformations. Among the 228 with information provided, 115 were in the treatment group and 113 in the control group. Entry criteria: Gestational age equal or less than 32 weeks, admitted from January 1984 to September 1985. Exclusion criteria: none described before randomization.
Interventions	Treatment: alpha-tocopheryl acetate (Ephynal) 20 mg/kg given intramuscularly daily for three doses commencing within two hours after randomization (first day of life). Controls: no injection
Outcomes	Mortality, periventricular-intraventricular hemorrhage, worsening of the intracranial hemorrhage, inflammation at site of injection
Notes	Mothers of some infants were part of another randomized trial. They were allocated either to vitamin E 400 mg every 4-6 hours or to placebo capsules during preterm labor. Plasma tocopherol level: treatment group $2.99 \pm 1.00$ mg/dl, control group $0.42 \pm 0.14$ mg/dl. Outcome variables are available only after eliminating patients with lethal malformations. Outcome variable available only in the 210 patients with negative initial scan: complete information about the grade of the intracranial hemorrhage

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Smith 1985**

Methods	Design: Randomized double-blind trial. Method of randomization: not provided. Blinding of intervention: yes. Complete follow-up: yes. Blinding of outcome: yes.
Participants	Total number of patients entered into the study: 30. Treatment group: 17, control group: 13. Entry criteria: gestational age 30-36 weeks, birth weight 970-2610 g, healthy, lack of pulmonary disease or oxygen requirement, no ABO or Rh isoimmunization, no other sources of bilirubin production, such as hematoma or bruising. Exclusion criteria: infection.
Interventions	Treatment: dl-alpha-tocopheryl polyethylene glycol-succinate (Mead Johnson) 50 mg/day orally once a day for 3 consecutive days, starting before 24 hours of life. Control: placebo.
Outcomes	Bilirubin, hemoglobin
Notes	Plasma tocopherol level: treatment group $2.11 \pm 0.79$ mg/dl, control group $1.71 \pm 1.40$ mg/dl

***Risk of bias***

**Smith 1985** (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Zipursky 1987**

Methods	Design: Randomized double-blind trial. Method of randomization: computer-generated randomization in the pharmacy, stratified by severity of illness. Blinding of intervention: yes. Complete follow-up: no; chronic lung disease information in 266; eye examination in 225 infants; hematologic data in 90 treated patients and 88 controls . Blinding of outcome: yes.
Participants	Total number of patients entered into the study: 269. Treatment group: 135, control group: 134. Entry criteria: birth weight < 1500 g, expected survival greater than 48 hours, informed consent. Exclusion criteria: major congenital anomalies, Rhesus hemolytic disease. Age at entry into the trial: 2.7±3 days in treatment group and 2.9±2 days in control group.
Interventions	Treatment: 25 IU tocopherol provided by gavage as 16 mg dl-alpha-tocopherol (Hoffman-La Roche) started day one, daily for six weeks. Control: placebo: drug vehicle (Tween 80).
Outcomes	Mortality in NICU, bronchopulmonary dysplasia, retinopathy of prematurity, hemoglobin, reticulocyte count, platelet count, coagulation tests
Notes	Plasma tocopherol level at six weeks: treatment group 2.88±2.02 mg/dl, control group 0.86±0.50 mg/dl. Outcome variables available only in subsets: hemoglobin concentration, reticulocyte count, platelet count, and coagulation tests

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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

Barnes 1968	Quasi-randomized trial assessing the effect of adding a small amount of vitamin E (11.5 mg per quart) to the formula on plasma tocopherol level, hemoglobin concentration and reticulocyte count measured in very low birth weight infants.
Chadd 1970	Randomized double blind placebo controlled trial of vitamin E for treatment of anemia of prematurity. Variability of hemoglobin is not provided.
Chirico 1983	None of the outcomes selected for this systematic review was analyzed. Outcome variables in this study included various in vitro indices of white cell function.

(Continued)

Conway 1986	<p>None of the outcomes selected for this systematic review could be analyzed using standard (parametric) meta-analysis, because the authors only provided medians and ranges, without means and standard deviations or percentages.</p> <p>Nevertheless, this double-blind randomized trial showed that adding either five or fifteen mg of vitamin E daily for ten weeks did not affect hemoglobin concentration, reticulocyte count of platelet count in preterm infants with a birth weight &lt; 1760 g. All infants received at least the minimum of vitamin E recommended, i.e., a vitamin E: PUFA ratio at least equal to 0.6. No infant received iron supplementation. No infant developed clinical or hematological sign of vitamin E deficiency.</p>
Curran 1979	<p>Quasi-randomized trial assessing the effect of three intramuscular injections of 50 mg/kg of Vitamin E Injectable (Roche) on days zero (&lt; six hours of life), one and two of life on retinopathy of prematurity in very low birth weight infants.</p>
Dyggve 1963	<p>Quasi-randomized trial assessing the effect of one intramuscular injection of 100 mg of al-alpha-tocopherol in aqueous colloidal solution (Ephynal, Hoffman-La Roche) just after birth on hemolysis in preterm infants. Entry criteria were prematurity and birth weight equal or less than 2,500 g.</p>
Ehrenkranz 1978	<p>Quasi-randomized trial assessing the effect of daily intramuscular injections of 20 mg/kg of vitamin E Injectable (Hoffmann-LaRoche), starting upon admission to the study and continued as long as inspiratory oxygen concentration was greater than 40%. Entry criteria included respiratory distress syndrome, inspiratory oxygen concentration greater than 40% and continuous distending pressure required to maintain arterial oxygen tension greater than 50 mm Hg.</p>
Fermanian 1976	<p>None of the outcomes selected for this systematic review could be analyzed using meta-analysis because standard deviation or standard error is not provided. This is a double-blind randomized trial assessing the effect of daily oral supplementation of 10 mg dl alpha-tocopheryl acetate (Ephynal, Roche) from the eighth day of life until nineteen weeks of life on hematologic parameters in preterm infants with a birth weight equal or less than 2500 g. Controls received placebo (lactose). Both vitamin E and placebo were dissolved in the milk. Infants were fed banked breast milk until reaching a weight of 1800 g (vitamin E content 9 mg/100 ml) and then formula (no measurable vitamin E). Iron was not provided. Among 74 infants entered into the study, 37 were randomized to treatment and 37 to control. Outcome measurements included hemoglobin concentration, hematocrit and reticulocyte count at seven weeks of life.</p>
Finer 1983	<p>This study included three groups: a historical control group (1978-81), and two vitamin E groups (1982). The early vitamin E group was given vitamin E orally before 12 hours of age by design, while late administration of vitamin E (after 40 hours) in the late vitamin E group was usually the result of an oversight.</p>
Gerl6czy 1949	<p>This study compares several consecutive cohorts.</p>
Goldbloom 1963	<p>No variability provided for the outcome variable, hemoglobin, at the end of the study. This is a quasi randomized trial comparing the effect of oral supplementation of vitamin E on hemoglobin concentration in healthy preterm infants. The trial had three arms, receiving, respectively, a vitamin E-free formula, a formula containing 3 mg/L of alpha tocopherol, and a formula supplemented to a total content of 8 mg per liter. The total number of enrolled patients was 44, including 14, 14 and 16 patients, respectively. Mean birth weights were, respectively, 1808±349 g, 1902±282 g, and 1732±242 g. Mean hemoglobin values were similar in all three arms at the end of the study.</p>

(Continued)

González-Corbella 98	This study was done in full-term infants. None of the outcomes selected for this systematic review was analyzed.
Gross 1974	Variability of the outcome variable (hemoglobin) is not provided. This study included a quasi-randomized trial and a randomized trial, both comparing the effects of water-soluble and fat-soluble vitamin E in preterm infants on hemoglobin concentration, vitamin E levels and erythrocyte phospholipids.
Gutcher 1985	None of the outcomes selected for this systematic review was analyzed. Outcome variables in this study included vitamin E level and percent peroxide-induced hemolysis.
Hashim 1968	This study compares breast milk, cotton seed formula and evaporated milk. The difference in vitamin E content (18 mg/quart in the two formulas and 12 mg/quart in breast milk) is only one of several major differences in milk composition. The authors do not provide the variability in hemoglobin and reticulocyte counts.
Hassan 1966	Quasi-randomized trial comparing two formulae and assessing the effects of vitamin E supplementation. Entry criteria were birth weight 940-2150 g, absence of congenital defects, and uncomplicated neonatal course.
Hervei 1983	Quasi-randomized trial assessing the effect of daily intramuscular injections of dl-alpha-tocopheryl acetate (Ephynal, Hoffmann-La Roche) 50 mg/kg/day from the first day of life until two weeks of age on blindness secondary to retrolental fibroplasia in preterm infants with birth weight equal or less than 1500 g.
Hittner 1983	This study compares two consecutive cohorts.
Huston 1982	Randomized allocation to either total parenteral nutrition with Intralip or total parenteral nutrition without Intralipid. Vitamin E was a co-intervention.
Jansson 1984	None of the outcomes selected for this systematic review was analyzed. The outcome variable in this study was serum vitamin E level.
Johnson 1974	Quasi-randomized trial assessing the effect of intramuscular administration of vitamin E on retrolental fibroplasia in preterm infants. Entry criteria included birth weight less than 2001 g regardless of oxygen need or birth weight over 2001 g with gestational age less than 36 weeks if oxygen required for over 24 hours, and informed consent.
Johnson 1982	These studies compare either (1) non simultaneous cohorts assigned, respectively, to vitamin E or no treatment or (2) combined data from two different protocols run in 1972-74 and 1974-76, respectively. These studies are also reported in Ann NY Acad Sci 1982 (see Johnson 1974 in included studies).
Johnson 1995	This study compared a group of patients with threshold retinopathy of prematurity treated with cryotherapy and vitamin E (1985-91) in one hospital with a non simultaneous group of patients treated with cryotherapy and no vitamin E in a multicenter trial (CRYO-ROP, 1986-7).
Kinsey 1951	This study compares several consecutive cohorts.
Levene 1979	Quasi randomized trial assessing hemoglobin and reticulocyte count. No data provided.

(Continued)

Lo 1973	Quasi randomized trial comparing three methods of treating hemolysis in preterm infants: vitamin E at the first sign of hemolysis, vitamin E within 2-4 weeks after developing hemolytic anemia, and no treatment. Averages and standard deviations of hemoglobin and reticulocyte count are provided only for the first group.
MacDonald 1987	This study describes two consecutive cohorts assigned, respectively, to MVI-Concentrate and 50 mg/week of intramuscular vitamin E, and to MVI-Pediatric 65% of a vial per day.
McWhirter 1974	No variability is provided for the outcome variable, i.e., hemoglobin.
Nishida 1986	None of the outcomes selected for this systematic review was analyzed. The outcome variables in this study were vitamin E levels in various eye compartments.
Oski 1967	Quasi-randomized trial assessing the effect of enteral vitamin E, beginning on the third day of life on hematologic parameters in preterm infants.
Owens 1949	Quasi-randomized trial assessing the effect of enteral vitamin E on retrolental fibroplasia in infants with a birth weight less than or equal to 1360 grams.
Panos 1968	Comparison of the outcome variable (hemoglobin) among groups is not possible because either standard deviation is not provided, or not all individual data are provided.
Sartain 1967	No data are provided in the published abstract.
Schwalbe 1992	None of the outcomes selected for this systematic review was analyzed. The outcome variable in this study was serum free alpha-tocopherol level.
Stone 2003	No preterm infants were enrolled and none of the outcomes selected for this systematic review were analyzed.
Zöberlein 1982	This study included both full-term and preterm infants.

## DATA AND ANALYSES

### Comparison 1. Vitamin E versus placebo or no vitamin E

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality until discharge	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All infants in all studies	12	2028	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.14]
1.2 Birth weight > 1000 grams	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.34, 2.62]
1.3 Enteral	3	445	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.63, 1.35]
1.4 Enteral hypertonic formulation, at pharmacologic doses	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.62, 1.46]
1.5 Parenteral with or without enteral	9	1583	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.17]
1.6 Parenteral with hypertonic enteral formulation at pharmacologic dose	5	1247	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.20]
1.7 Intravenous (with or without other routes of administration)	2	832	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.82, 1.32]
1.8 Excluding intravenous vitamin E administration	10	1196	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.14]
1.9 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	5	575	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.60, 1.34]
1.10 Total dose of vitamin E in the treatment group > 30 IU/kg/day	6	1396	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.17]
1.11 Serum tocopherol level in the treatment group <= 3.5 mg/dl	7	1157	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.19]
1.12 Serum tocopherol level in the treatment group >3.5 mg/dl	5	871	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.80, 1.24]
1.13 Onset of vitamin E supplementation in the treatment group within 48 hours of life	11	1998	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.14]
1.14 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.15 Duration of treatment <= 1 week (7 days)	4	475	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.56, 1.18]
1.16 Duration of treatment > 1 week	7	1008	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.28]
1.17 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	9	1613	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.19]

1.18 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	3	415	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.68, 1.24]
1.19 Iron supplementation > 2 mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.20 Iron supplementation > 2 mg/kg/day in neither group	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.40, 1.85]
1.21 PUFA >= 400 mg/100 ml milk	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.40, 1.85]
2 Mortality until discharge among very low birth weight infants	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 All infants in all studies	7	1334	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.16]
2.2 Birth weight <= 1500 grams	6	1187	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.75, 1.15]
2.3 Birth weight > 1000 grams	2	496	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.74, 1.67]
2.4 Birth weight <= 1000 grams	4	449	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.17]
2.5 Enteral	3	445	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.63, 1.35]
2.6 Enteral hypertonic formulation, at pharmacologic doses	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.62, 1.46]
2.7 Parenteral with or without enteral	4	889	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.79, 1.21]
2.8 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.38, 1.24]
2.9 Intravenous (with or without other routes of administration)	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.34]
2.10 Excluding intravenous vitamin E supplementation	6	789	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.19]
2.11 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	268	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.40, 1.85]
2.12 Total dose of vitamin E in the treatment group > 30 IU/kg/day	4	1009	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.18]
2.13 Serum tocopherol level in the treatment group <= 3.5 mg/dl	5	642	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.17]
2.14 Serum tocopherol level in the treatment group >3.5 mg/dl	2	692	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.82, 1.31]
2.15 Onset of vitamin E supplementation in the treatment group within 48 hours of life	6	1304	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.16]
2.16 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.17 Duration of treatment <= 1 week (7 days)	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.38, 1.24]



2.18 Duration of treatment > 1 week	6	1166	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.83, 1.23]
2.19 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	5	1019	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.78, 1.23]
2.20 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	2	315	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.67, 1.29]
2.21 Iron supplementation > 2 mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.22 Iron supplementation > 2 mg/kg/day in neither group	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.40, 1.85]
2.23 PUFA >= 400 mg/100 ml milk	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.40, 1.85]
3 Bronchopulmonary dysplasia	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 All infants in all studies	6	1127	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.73, 1.14]
3.2 Enteral	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]
3.3 Parenteral with or without enteral	6	912	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.75, 1.23]
3.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	3	771	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.20]
3.5 Intravenous (with or without other routes of administration)	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.21]
3.6 Excluding intravenous vitamin E administration	5	582	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.31]
3.7 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	4	498	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.63, 1.38]
3.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	680	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.71, 1.22]
3.9 Serum tocopherol level in the treatment group <= 3.5 mg/dl	3	352	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.56, 1.50]
3.10 Serum tocopherol level in the treatment group > 3.5 mg/dl	4	826	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.20]
3.11 Onset of treatment within 48 hours of life	7	1178	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.74, 1.16]
3.12 Duration of treatment <= 1 week	3	141	Risk Ratio (M-H, Fixed, 95% CI)	6.04 [0.30, 119.88]
3.13 Duration of treatment > 1 week	3	492	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.31]
3.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	6	1078	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.16]
3.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.49, 2.60]

3.16 Iron supplementation >2 mg/kg/day in both groups	1	10	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.17 Iron supplementation > 2 mg/kg/day in neither group	2	291	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]
3.18 PUFA >= 400 mg/100 ml milk	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]
3.19 Vitamin A supplementation in both groups >= 1500 IU/day	1	35	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Bronchopulmonary dysplasia among very low birth weight infants	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 All infants in all studies	4	972	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.13]
4.2 Enteral	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]
4.3 Parenteral with or without enteral	3	706	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.70, 1.19]
4.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.21]
4.5 Intravenous (with or without other routes of administration)	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.21]
4.6 Excluding intravenous	3	427	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.30]
4.7 Total dose of vitamin E <= 30 IU/kg/day	2	392	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.30]
4.8 Total dose of vitamin E > 30 IU/kg/day	2	580	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.21]
4.9 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	301	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]
4.10 Serum tocopherol level in the treatment group > 3.5 mg/dl	2	671	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.70, 1.19]
4.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	4	972	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.13]
4.12 Duration of treatment <= 1 week	1	35	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.13 Duration of treatment > 1 week	2	392	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.30]
4.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	4	972	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.13]
4.15 Iron supplementation >2 mg/kg/day in both groups	1	10	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.16 Iron supplementation > 2 mg/kg/day in neither group	2	291	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]
4.17 PUFA >= 400 mg/100 ml milk	1	266	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]

4.18 Vitamin A supplementation in both groups $\geq$ 1500 IU/day	1	35	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Bronchopulmonary dysplasia among surviving patients	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 All infants in all studies	4	322	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.84, 1.58]
5.2 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.63, 2.21]
5.3 Enteral hypertonic formulation at pharmacologic dose	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.63, 2.21]
5.4 Parenteral with or without enteral	3	221	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.80, 1.64]
5.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.55, 1.76]
5.6 Excluding intravenous vitamin E administration	4	322	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.84, 1.58]
5.7 Total dose of vitamin E in the treatment group $\leq$ 30 IU/kg/day	2	86	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.91, 2.02]
5.8 Total dose of vitamin E in the treatment group $>$ 30 IU/kg/day	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.70, 1.64]
5.9 Serum tocopherol level in the treatment group $\leq$ 3.5 mg/dl	3	287	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.75, 1.74]
5.10 Serum tocopherol level in the treatment group $>$ 3.5 mg/dl	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.82, 1.71]
5.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	4	322	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.84, 1.58]
5.12 Duration of treatment $\leq$ 1 week (7 days)	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.64, 1.96]
5.13 Duration of treatment $>$ 1 week	2	136	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.81, 1.71]
5.14 Total dose of vitamin E in the control group $>$ 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.55, 1.76]
5.15 Total dose of vitamin E in the control group $\leq$ 10 mg vit E/100 kcal	3	187	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.87, 1.83]
5.16 Iron supplementation $>$ 2 mg/kg/day in both groups	1	51	Risk Ratio (M-H, Fixed, 95% CI)	6.04 [0.30, 119.88]
6 Bronchopulmonary dysplasia among surviving very low birth weight infants	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 All infants in all studies	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.70, 1.64]
6.2 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.63, 2.21]

6.3 Enteral hypertonic formulation at pharmacologic dose	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.63, 2.21]
6.4 Parenteral with or without enteral	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.55, 1.76]
6.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.55, 1.76]
6.6 Excluding intravenous vitamin E administration	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.70, 1.64]
6.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.70, 1.64]
6.8 Serum tocopherol level in the treatment group <=3.5 mg/dl	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.70, 1.64]
6.9 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.70, 1.64]
6.10 Duration of treatment <=1 week (7 days)	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.55, 1.76]
6.11 Duration of treatment > 1 week	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.63, 2.21]
6.12 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.55, 1.76]
6.13 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.63, 2.21]
7 Radiographic signs of bronchopulmonary dysplasia persistent at 6 weeks - 2 months	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 All infants in all studies	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.67, 1.46]
7.2 Enteral	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]
7.3 Parenteral with or without enteral	2	226	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.62, 1.70]
7.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	226	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.62, 1.70]
7.5 Excluding intravenous vitamin E administration	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.67, 1.46]
7.6 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
7.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.49, 2.60]
7.8 Serum tocopherol level in the treatment group <=3.5 mg/dl	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]

7.9 Serum tocopherol level in the treatment group >3.5 mg/dl	2	226	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.62, 1.70]
7.10 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.67, 1.46]
7.11 Duration of treatment > 1 week	3	364	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.67, 1.46]
7.12 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
7.13 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.49, 2.60]
7.14 Iron supplementation >2 mg/kg/day in neither group	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]
7.15 PUFA >= 400 mg/100 ml milk	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]
8 Radiographic signs of bronchopulmonary dysplasia at 6 weeks - 2 months among very low birth weight infants	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 All infants in all studies	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
8.2 Birth weight <= 1500 grams	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
8.3 Birth weight <= 1000 grams	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.72, 2.17]
8.4 Birth weight > 1000 grams	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.09, 2.46]
8.5 Enteral	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]
8.6 Parenteral with or without enteral	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.51, 1.83]
8.7 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.51, 1.83]
8.8 Excluding intravenous vitamin E administration	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
8.9 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
8.10 Serum tocopherol level in the treatment group <=3.5 mg/dl	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]
8.11 Serum tocopherol level in the treatment group >3.5 mg/dl	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.51, 1.83]
8.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]

8.13 Duration of treatment > 1 week	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
8.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.47]
8.15 Iron supplementation >2 mg/kg/day in neither group	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]
8.16 PUFA >= 400 mg/100 ml milk	1	138	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.51, 1.72]
9 Patent ductus arteriosus	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 All infants in all studies	6	976	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.93, 1.23]
9.2 Parenteral with or without enteral	6	976	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.93, 1.23]
9.3 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	918	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.25]
9.4 Intravenous (with or without other routes of administration)	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.31]
9.5 Excluding intravenous vitamin E administration	5	431	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.28]
9.6 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	3	184	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.75, 1.38]
9.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	792	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.26]
9.8 Serum tocopherol level in the treatment group <=3.5 mg/dl	2	58	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.69, 1.45]
9.9 Serum tocopherol level in the treatment group >3.5 mg/dl	4	918	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.25]
9.10 Onset of vitamin E supplementation in the treatment group within 48 hours of life	5	947	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.24]
9.11 Duration of treatment > 1 week	5	431	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.28]
9.12 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	4	729	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.92, 1.25]
9.13 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	2	247	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.77, 1.42]
10 Patent ductus arteriosus among very low birth weight infants	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 All infants in all studies	4	847	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.28]
10.2 Birth weight <= 1500 grams	3	700	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.27]

10.3 Birth weight <= 1000 grams	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.55, 2.81]
10.4 Parenteral with or without enteral	4	847	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.28]
10.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.31]
10.6 Intravenous with or without other routes of administration	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.31]
10.7 Excluding intravenous administration	3	302	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.78, 1.54]
10.8 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	155	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.73, 1.52]
10.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	692	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.93, 1.31]
10.10 Serum tocopherol level in the treatment group <= 3.5 mg/dl	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.66, 1.87]
10.11 Serum tocopherol level in the treatment group >3.5 mg/dl	3	818	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.29]
10.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	4	847	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.28]
10.13 Duration of treatment > 1 week	3	302	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.78, 1.54]
10.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	3	700	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.27]
10.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.55, 2.81]
11 Patent ductus arteriosus among surviving patients (at 10 days-10 weeks)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 All infants in all studies	3	271	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.38]
11.2 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.35, 2.28]
11.3 Enteral hypertonic formulation at pharmacologic doses	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.35, 2.28]
11.4 Parenteral with or without enteral	2	170	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.70, 1.44]
11.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
11.6 Excluding intravenous administration	3	271	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.38]



11.7 Total dose of vitamin E in the treatment group ≤ 30 IU/kg/day	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.84, 3.12]
11.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]
11.9 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]
11.10 Serum tocopherol level in the treatment group >3.5 mg/dl	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.84, 3.12]
11.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	271	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.38]
11.12 Duration of treatment ≤ 1 week (7 days)	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
11.13 Duration of treatment > 1 week	2	136	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.72, 2.14]
11.14 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	2	136	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.72, 2.14]
11.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
12 Patent ductus arteriosus among surviving very low birth infants (at 10 days-10 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 All infants in all studies	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]
12.2 Birth weight ≤ 1500 grams	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]
12.3 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.35, 2.28]
12.4 Enteral hypertonic formulation at pharmacologic doses	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.35, 2.28]
12.5 Parenteral with or without enteral	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
12.6 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
12.7 Excluding intravenous administration	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]
12.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]
12.9 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]

12.10 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]
12.11 Duration of treatment <= 1 week (7 days)	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
12.12 Duration of treatment > 1 week	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.35, 2.28]
12.13 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.35, 2.28]
12.14 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.54, 1.31]
13 Patent ductus arteriosus requiring treatment	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 All infants in all studies	3	675	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.31]
13.2 Enteral	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
13.3 Parenteral with or without enteral	2	645	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.32]
13.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	645	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.32]
13.5 Intravenous (with or without other routes of administration)	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
13.6 Excluding intravenous treatment	2	130	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.97]
13.7 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
13.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	645	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.32]
13.9 Serum tocopherol level in the treatment group <= 3.5 mg/dl	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
13.10 Serum tocopherol level in the treatment group >3.5 mg/dl	2	645	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.32]
13.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	645	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.32]
13.12 Duration of treatment > 1 week	2	130	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.97]
13.13 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	575	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.60]

13.14 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.31, 0.95]
13.15 Iron supplementation > 2 mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
14 Patent ductus arteriosus requiring treatment among very low birth weight infants	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 All infants in all studies	2	575	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.60]
14.2 Birth weight <= 1500 grams	2	575	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.60]
14.3 Enteral	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
14.4 Parenteral with or without enteral	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
14.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
14.6 Intravenous (with or without other routes of administration)	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
14.7 Excluding intravenous treatment	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
14.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
14.9 Serum tocopherol level in the treatment group <= 3.5 mg/dl	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
14.10 Serum tocopherol level in the treatment group >3.5 mg/dl	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
14.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
14.12 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
14.13 Duration of treatment > 1 week	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
14.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	575	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.60]
14.15 Iron supplementation > 2 mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
15 Sepsis after study entry	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 All infants in all studies	4	1009	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.13, 2.04]
15.2 Enteral	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
15.3 Parenteral with or without enteral	3	979	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.15, 2.14]

15.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	3	979	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.15, 2.14]
15.5 Intravenous	2	832	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.07, 2.21]
15.6 Excluding intravenous vitamin E administration	2	177	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.90, 2.46]
15.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	979	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.15, 2.14]
15.8 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	317	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.45, 1.77]
15.9 Serum tocopherol level in the treatment group > 3.5 mg/dl	2	692	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.24, 2.40]
15.10 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	979	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.15, 2.14]
15.11 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
15.12 Duration of treatment > 1 week	3	464	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.82, 1.96]
15.13 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	3	862	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.05, 2.08]
15.14 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.93, 2.98]
15.15 Iron supplementation > 2mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
16 Sepsis after study entry among very low birth weight infants	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 All infants in all studies	4	807	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.13, 2.08]
16.2 Birth weight <= 1500 grams	2	575	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.13, 2.40]
16.3 Birth weight <= 1000 grams	2	232	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.79, 2.22]
16.4 Enteral	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
16.5 Parental with or without enteral	3	777	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.15, 2.18]
16.6 Parenteral with hypertonic enteral formulation at pharmacologic dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.7 Intravenous	2	630	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.07, 2.27]
16.8 Excluding intravenous vitamin E supplementation	3	326	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.86, 2.12]
16.9 Total dose of vitamin E supplementation in the treatment group > 30 IU/kg/day	3	777	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.15, 2.18]

16.10 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.33, 1.64]
16.11 Serum tocopherol level in the treatment group > 3.5 mg/dl	2	692	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.24, 2.40]
16.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	777	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.15, 2.18]
16.13 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
16.14 Duration of treatment > 1 week	3	262	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.79, 1.99]
16.15 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	3	660	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.04, 2.13]
16.16 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.93, 2.98]
16.17 Iron supplementation > 2mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
17 Sepsis after study entry among very low birth weight infants treated for > 1 week	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 All infants in all studies	4	726	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.17, 2.26]
17.2 Birth weight <= 1500 grams	3	641	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.27, 2.53]
17.3 Birth weight <= 1000 grams	2	232	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.79, 2.22]
17.4 Enteral	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
17.5 Parental with or without enteral	3	696	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.20, 2.41]
17.6 Intravenous	2	549	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.11, 2.66]
17.7 Excluding intravenous vitamin E supplementation	2	177	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.90, 2.46]
17.8 Total dose of vitamin E supplementation in the treatment group > 30 IU/kd/day	3	696	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.20, 2.41]
17.9 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.33, 1.64]
17.10 Serum tocopherol level in the treatment group > 3.5 mg/dl	2	611	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.31, 2.75]
17.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	696	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.20, 2.41]

17.12 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
17.13 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	3	579	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.08, 2.41]
17.14 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.93, 2.98]
17.15 Iron supplementation > 2mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
18 Sepsis among surviving very low birth weight infants	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 All infants in all studies	2	284	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.48, 1.62]
18.2 Enteral	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.36, 2.67]
18.3 Enteral hypertonic formulation, at pharmacologic doses	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.36, 2.67]
18.4 Parenteral with or without enteral	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.38, 1.77]
18.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.38, 1.77]
18.6 Excluding intravenous vitamin E administration	2	284	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.48, 1.62]
18.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	284	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.48, 1.62]
18.8 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	284	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.48, 1.62]
18.9 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	284	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.48, 1.62]
18.10 Duration of treatment <= 1 week	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.38, 1.77]
18.11 Duration of treatment > 1 week	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.36, 2.67]
18.12 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.36, 2.67]
18.13 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.38, 1.77]
19 Germinal matrix/ intraventricular hemorrhage (grades I-IV)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 All infants in all studies	7	1755	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 0.99]
19.2 Birth weight >= 1000 grams	1	760	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.78, 2.14]

19.3 Parenteral with or without enteral	7	1755	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.72, 0.98]
19.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	1448	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.12]
19.5 Intravenous (with or without other routes of administration)	2	1201	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.28]
19.6 Excluding intravenous administration	5	554	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.58, 0.87]
19.7 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	3	307	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.50, 0.85]
19.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	4	1448	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.12]
19.9 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	515	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.67, 1.00]
19.10 Serum tocopherol level in the treatment group >3.5 mg/dl	5	1240	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.08]
19.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	7	1755	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 0.99]
19.12 Duration of treatment <= 1 week	3	307	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.50, 0.85]
19.13 Duration of treatment > 1 week	3	534	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.71, 1.09]
19.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	5	1508	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.03]
19.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	2	247	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.04]
20 Germinal matrix/ intraventricular hemorrhage among very low birth weight infants	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 All infants in all studies	3	777	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.18]
20.2 Birth weight <= 1500 grams	1	545	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.46]
20.3 Birth weight <= 1000 grams	3	377	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.11]
20.4 Birth weight 1001-1500 grams	1	393	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.69, 2.11]
20.5 Parenteral with or without enteral	3	777	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.18]

20.6 Parenteral with hypertonic enteral formulation at pharmacologic dose	3	777	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.18]
20.7 Intravenous (with or without other routes of administration)	2	630	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.81, 1.40]
20.8 Excluding intravenous administration	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.46, 1.04]
20.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	777	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.18]
20.10 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.85, 1.68]
20.11 Serum tocopherol level in the treatment group >3.5 mg/dl	2	692	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.65, 1.14]
20.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	777	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.18]
20.13 Duration of treatment > 1 week	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
20.14 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	2	630	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.81, 1.40]
20.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.46, 1.04]
21 Germinal matrix/ intraventricular hemorrhage among patients with negative initial ultrasonogram	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 All infants in all studies	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.40, 0.80]
22 Germinal matrix/ intraventricular hemorrhage among survivors	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 All infants in all studies	3	335	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.60]
22.2 Enteral	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.68, 2.36]
22.3 Enteral hypertonic formulation at pharmacologic doses	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.68, 2.36]
22.4 Parenteral with or without enteral	2	186	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.52, 1.58]
22.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.57]
22.6 Excluding intravenous administration	3	335	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.60]



22.7 Total dose of vitamin E in the treatment group ≤ 30 IU/kg/day	1	51	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.19, 7.98]
22.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	284	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
22.9 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	3	335	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.60]
22.10 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	335	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.60]
22.11 Duration of treatment ≤ 1 week	2	186	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.52, 1.58]
22.12 Duration of treatment > 1 week	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.68, 2.36]
22.13 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	2	200	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.70, 2.28]
22.14 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.57]
23 Germinal matrix/ intraventricular hemorrhage among surviving very low birth weight infants	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 All infants in all studies	2	284	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
23.2 Birth weight ≤ 1500 grams	2	284	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
23.3 Birth weight ≤ 1000 grams	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.40, 2.17]
23.4 Enteral	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.68, 2.36]
23.5 Enteral hypertonic formulation at pharmacologic doses	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.68, 2.36]
23.6 Parenteral with or without enteral	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.57]
23.7 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.57]
23.8 Excluding intravenous administration	2	284	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
23.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	284	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
23.10 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	2	284	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]

23.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	284	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
23.12 Duration of treatment <= 1 week	2	186	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.52, 1.58]
23.13 Duration of treatment > 1 week	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.68, 2.36]
23.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	200	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.70, 2.28]
23.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.57]
24 Severe intraventricular hemorrhage (grade III-IV)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 All infants in all studies	3	644	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.60, 1.38]
24.2 Parenteral with or without enteral	3	644	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.60, 1.38]
24.3 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
24.4 Intravenous (with or without other routes of administration)	1	287	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.88, 2.96]
24.5 Excluding intravenous vitamin E supplementation	2	357	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.28, 0.94]
24.6 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.42]
24.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
24.8 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	497	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.70, 2.05]
24.9 Serum tocopherol level in the treatment group > 3.5 mg/dl	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.15]
24.10 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	644	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.60, 1.38]
24.11 Duration of treatment <= 1 week	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.42]
24.12 Duration of treatment > 1 week	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
24.13 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	497	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.70, 2.05]

24.14 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.15]
25 Severe intraventricular hemorrhage among very low birth weight infants	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
25.1 All infants in all studies	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
25.2 Birth weight <= 1000 grams	2	232	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.63, 1.78]
25.3 Parenteral with or without enteral	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
25.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
25.5 Intravenous (with or without other routes of administration)	1	287	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.88, 2.96]
25.6 Excluding intravenous vitamin E supplementation	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.15]
25.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
25.8 Serum tocopherol level in the treatment group <= 3.5 mg/dl	1	287	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.88, 2.96]
25.9 Serum tocopherol level in the treatment group > 3.5 mg/dl	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.15]
25.10 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
25.11 Duration of treatment > 1 week	2	434	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.67, 1.60]
25.12 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	1	287	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.88, 2.96]
25.13 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.15]
26 Severe intraventricular hemorrhage among surviving very low birth weight infants	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 All infants in all studies	3	320	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.41, 1.39]
26.2 Birth weight <= 1500 grams	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.62, 2.66]
26.3 Birth weight <= 1000 grams	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.10, 0.92]
26.4 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.62, 3.19]

26.5 Enteral hypertonic formulation at pharmacologic dose	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.62, 3.19]
26.6 Parenteral with or without enteral	2	219	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.02]
26.7 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	219	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.02]
26.8 Excluding intravenous vitamin E supplementation	3	320	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.41, 1.39]
26.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	320	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.41, 1.39]
26.10 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.62, 2.66]
26.11 Serum tocopherol level in the treatment group > 3.5 mg/dl	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.05, 0.85]
26.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	320	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.41, 1.39]
26.13 Duration of treatment <= 1 week	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.21, 4.71]
26.14 Duration of treatment > 1 week	2	185	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.37, 1.39]
26.15 Total dose of vitamin E in the control group <= 10 mg/100 kcal	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.62, 3.19]
26.16 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	2	219	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.14, 1.02]
27 Parenchymal hemorrhage (grade IV)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 All infants in all studies	2	497	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.69, 2.67]
27.2 Parenteral with or without enteral	2	497	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.69, 2.67]
27.3 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	287	Risk Ratio (M-H, Fixed, 95% CI)	2.4 [1.02, 5.66]
27.4 Intravenous (with or without other routes of administration)	1	287	Risk Ratio (M-H, Fixed, 95% CI)	2.4 [1.02, 5.66]
27.5 Excluding intravenous vitamin E administration	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.42]
27.6 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.42]

27.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	1	287	Risk Ratio (M-H, Fixed, 95% CI)	2.4 [1.02, 5.66]
27.8 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	497	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.69, 2.67]
27.9 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	497	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.69, 2.67]
27.10 Duration of treatment <= 1 week	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.42]
27.11 Duration of treatment > 1 week	1	287	Risk Ratio (M-H, Fixed, 95% CI)	2.4 [1.02, 5.66]
27.12 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	497	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.69, 2.67]
28 Parenchymal hemorrhage among very low birth weight infants	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 All infants in all studies	1	85	Risk Ratio (M-H, Fixed, 95% CI)	9.21 [1.22, 69.58]
28.2 Birth weight <= 1000 grams	1	85	Risk Ratio (M-H, Fixed, 95% CI)	9.21 [1.22, 69.58]
29 Parenchymal hemorrhage among patients with negative initial ultrasonogram	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 All infants in all studies	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.42]
30 Parenchymal hemorrhage (Grade IV) among surviving very low birth weight infants	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
30.1 All infants in all studies	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.46, 4.66]
30.2 Birth weight <= 1500 grams	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.46, 4.66]
30.3 Birth weight <= 1000 grams	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.01, 6.41]
30.4 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.54, 7.71]
30.5 Enteral hypertonic formulation at pharmacologic dose	1	101	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.54, 7.71]
30.6 Parenteral with or without enteral	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.92]
30.7 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.92]
30.8 Excluding intravenous vitamin E supplementation	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.46, 4.66]
30.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.46, 4.66]

30.10 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.46, 4.66]
30.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.46, 4.66]
30.12 Duration of treatment <= 1 week	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.92]
30.13 Duration of treatment > 1 week	1	101	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.54, 7.71]
30.14 Total dose of vitamin E in the control group <= 10 mg/100 kcal	1	101	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.54, 7.71]
30.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.92]
31 Retrolental fibroplasia/retinopathy of prematurity	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
31.1 All infants in all studies	7	1342	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.09]
31.2 Enteral	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.31]
31.3 Parenteral with or without enteral	5	973	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.11]
31.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	3	932	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.13]
31.5 Intravenous (with or without other routes of administration)	2	832	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.11]
31.6 Excluding intravenous vitamin E supplementation	5	510	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.50, 1.43]
31.7 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	3	374	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.31]
31.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	4	967	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.13]
31.9 Serum tocopherol level in the treatment group <= 3.5 mg/dl	4	641	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.59, 1.28]
31.10 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	700	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.13]
31.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	6	796	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.65, 1.32]
31.12 Duration of treatment <= 1 week	3	141	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
31.13 Duration of treatment > 1 week	3	655	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.65, 1.32]

31.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	6	1241	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.07]
31.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.53, 3.02]
31.16 Iron supplementation >2 mg/kg in both groups	2	61	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
31.17 Iron supplementation > 2 mg/kg in neither group	2	293	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.31]
31.18 Vitamin A supplementation in both groups >= 1500 IU/day	1	25	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
31.19 PUFA >= 400 mg/100 ml milk	1	269	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.35, 1.32]
32 Retrolental fibroplasia/retinopathy of prematurity among very low birth weight infants	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 All infants in all studies	5	975	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.07]
32.2 Birth weight <= 1500 grams	4	890	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.70, 1.05]
32.3 Birth weight <= 1000 grams	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.60, 2.53]
32.4 Enteral	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.31]
32.5 Parenteral with or without enteral	4	707	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.12]
32.6 Parenteral with hypertonic enteral formulation at pharmacologic dose	3	672	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.12]
32.7 Intravenous (with or without other routes of administration)	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.74, 1.13]
32.8 Excluding intravenous vitamin E supplementation	3	345	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.45, 1.24]
32.9 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.31]
32.10 Total dose of vitamin E in the treatment group > 30 IU/kg/day	4	707	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.12]
32.11 Serum tocopherol level in the treatment group <= 3.5 mg/dl	3	388	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.53, 1.40]
32.12 Serum tocopherol level in the treatment group > 3.5 mg/dl	2	587	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.72, 1.10]
32.13 Onset of vitamin E supplementation in the treatment group within 48 hours of life	5	975	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.07]

32.14 Duration of treatment ≤ 1 week	1	35	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
32.15 Duration of treatment > 1 week	3	395	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.32]
32.16 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	4	933	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.72, 1.08]
32.17 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.42, 1.96]
32.18 Iron supplementation >2 mg/kg in both groups	1	10	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
32.19 Iron supplementation > 2 mg/kg in neither group	2	293	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.31]
32.20 Vitamin A supplementation in both groups ≥ 1500 IU/day	1	35	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
32.21 PUFA ≥ 400 mg/100 ml milk	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.31]
33 Retrolental fibroplasia/ retinopathy of prematurity among infants examined/ survivors	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 All infants in all studies	8	1666	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.78, 1.03]
33.2 Enteral	2	354	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.66, 1.23]
33.3 Enteral hypertonic formulation at pharmacologic doses	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.72, 1.43]
33.4 Parenteral with or without enteral	5	1261	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
33.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	5	1261	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
33.6 Intravenous (with or without other routes of administration)	2	953	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.70, 1.04]
33.7 Excluding intravenous supplementation	6	713	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.15]
33.8 Total dose of vitamin E in the treatment group ≤ 30 IU/kg/day	2	324	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.45, 1.22]
33.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	5	1291	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.80, 1.06]
33.10 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	4	687	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.15]
33.11 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	928	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.69, 1.04]



33.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	7	1615	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.78, 1.03]
33.13 Duration of treatment <= 1 week	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.28]
33.14 Duration of treatment > 1 week	6	1480	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.74, 1.03]
33.15 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	5	1406	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.02]
33.16 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	2	209	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.83, 1.31]
33.17 Iron supplementation >2 mg/kg in both groups	1	51	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
33.18 Iron supplementation > 2 mg/kg in neither group	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.36, 1.35]
33.19 PUFA >= 400 mg/100 ml milk	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.36, 1.35]
34 Retrolental fibroplasia/retinopathy of prematurity among very low birth weight infants examined	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.1 All infants in all studies	7	1090	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.82, 1.07]
34.2 Birth weight <= 1500 grams	6	1054	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.81, 1.06]
34.3 Birth weight <= 1000 grams	3	84	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.29]
34.4 Birth weight > 1000 grams	3	181	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.76, 1.42]
34.5 Enteral	2	354	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.66, 1.23]
34.6 Enteral hypertonic formulation at pharmacologic doses	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.72, 1.43]
34.7 Parenteral with or without enteral	5	736	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.09]
34.8 Parenteral with hypertonic enteral formulation at pharmacologic dose	5	736	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.09]
34.9 Intravenous (with or without other routes of administration)	2	460	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.12]
34.10 Excluding intravenous supplementation	5	630	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.13]
34.11 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.36, 1.35]
34.12 Total dose of vitamin E in the treatment group > 30 IU/kg/day	6	865	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]

34.13 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	4	525	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
34.14 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	565	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.08]
34.15 Onset of vitamin E supplementation in the treatment group within 48 hours of life	7	1090	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.82, 1.07]
34.16 Duration of treatment ≤ 1 week	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.28]
34.17 Duration of treatment > 1 week	5	531	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.72, 1.18]
34.18 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	5	913	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.78, 1.07]
34.19 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	2	177	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.26]
34.20 Iron supplementation > 2 mg/kg in neither group	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.36, 1.35]
34.21 PUFA ≥ 400 mg/100 ml milk	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.36, 1.35]
35 Severe retrolental fibroplasia/retinopathy of prematurity (grade 3 or worse)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 All infants in all studies	6	1565	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.41, 1.25]
35.2 Enteral	1	29	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
35.3 Parenteral with or without enteral	5	1297	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.39, 1.37]
35.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	1268	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.41, 1.37]
35.5 Intravenous (with or without other routes of administration)	2	1042	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.43, 1.72]
35.6 Excluding intravenous vitamin E supplementation	4	523	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.20, 1.35]
35.7 Total dose of vitamin E in the treatment group ≤ 30 IU/kg/day	3	423	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.64]
35.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	1142	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.41, 1.52]
35.9 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	3	584	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.53, 2.31]
35.10 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	981	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.16, 1.00]

35.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	8	1882	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.40, 1.14]
35.12 Duration of treatment > 1 week	6	1565	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.41, 1.25]
35.13 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	5	1465	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.42, 1.35]
35.14 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.04, 3.49]
35.15 Iron supplementation > 2 mg/kg in neither group	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.14, 2.42]
35.16 PUFA >= 400 mg/100 ml milk	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.14, 2.42]
36 Severe retrolental fibroplasia/retinopathy of prematurity (grade >= 3) among very low birth weight infants	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
36.1 All infants in all studies	6	974	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.32, 1.08]
36.2 Birth weight <= 1500 grams	5	889	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.18, 0.87]
36.3 Birth weight <= 1000 grams	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.35, 2.10]
36.4 Enteral	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.14, 2.42]
36.5 Parenteral with or without enteral	5	706	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.16]
36.6 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	677	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.30, 1.16]
36.7 Intravenous (with or without other routes of administration)	2	509	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.34, 1.61]
36.8 Excluding intravenous vitamin E supplementation	4	465	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.16, 1.16]
36.9 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	3	423	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.19, 1.64]
36.10 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	551	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.29, 1.27]
36.11 Serum tocopherol level in the treatment group <= 3.5 mg/dl	3	382	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.44, 2.32]
36.12 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	592	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.13, 0.87]

36.13 Onset of vitamin E supplementation in the treatment group within 48 hours of life	6	974	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.32, 1.08]
36.14 Duration of treatment > 1 week	5	550	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.36, 1.43]
36.15 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	5	932	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.35, 1.25]
36.16 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.38]
36.17 Iron supplementation > 2 mg/kg in neither group	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.14, 2.42]
36.18 PUFA >= 400 mg/100 ml milk	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.14, 2.42]
37 Severe retrolental fibroplasia/retinopathy of prematurity (grade 3 or worse) among patients examined	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 All infants in all studies	7	1587	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.40, 1.12]
37.2 Enteral	2	326	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.10, 1.13]
37.3 Enteral hypertonic formulation at pharmacologic doses	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.63]
37.4 Parenteral or both parenteral and enteral	5	1261	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.46, 1.44]
37.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	1162	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.47, 1.60]
37.6 Intravenous (with or without other routes of administration)	2	953	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.42, 1.66]
37.7 Excluding intravenous vitamin E supplementation	5	634	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.24, 1.13]
37.8 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	324	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.20, 1.69]
37.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	5	1263	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.39, 1.26]
37.10 Serum tocopherol level in the treatment group <= 3.5 mg/dl	4	659	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.48, 1.69]
37.11 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	928	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.15, 0.98]
37.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	7	1587	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.40, 1.12]

37.13 Duration of treatment ≤ 1 week (7 days)	1	135	Risk Ratio (M-H, Fixed, 95% CI)	2.96 [0.32, 27.71]
37.14 Duration of treatment > 1 week	5	697	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.39, 1.26]
37.15 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	5	1378	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.36, 1.10]
37.16 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	2	209	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.25, 3.89]
37.17 Iron supplementation > 2 mg/kg in neither group	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.52]
37.18 PUFA ≥ 400 mg/100 ml milk	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.52]
38 Severe retrolental fibroplasia/ retinopathy of prematurity among very low birth weight infants examined	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 All infants in all studies	7	1062	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.34, 1.00]
38.2 Birth weight ≤ 1500 grams	6	1026	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.22, 0.85]
38.3 Birth weight ≤ 1000 grams	3	94	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.48, 2.19]
38.4 Birth weight > 1000 grams	3	181	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 8.39]
38.5 Enteral	2	326	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.10, 1.13]
38.6 Enteral hypertonic formulation at pharmacologic doses	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.63]
38.7 Parenteral or both parenteral and enteral	5	736	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.38, 1.28]
38.8 Parenteral with hypertonic enteral formulation at pharmacologic dose	5	736	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.38, 1.28]
38.9 Intravenous (with or without other routes of administration)	2	460	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.35, 1.52]
38.10 Excluding intravenous vitamin E supplementation	5	602	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.22, 1.04]
38.11 Total dose of vitamin E in the treatment group ≤ 30 IU/kg/day	2	324	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.20, 1.69]
38.12 Total dose of vitamin E in the treatment group > 30 IU/kg/day	5	738	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.32, 1.09]
38.13 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	4	497	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.42, 1.61]
38.14 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	565	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.13, 0.88]

38.15 Onset of vitamin E supplementation in the treatment group within 48 hours of life	7	1062	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.34, 1.00]
38.16 Duration of treatment <= 1 week (7 days)	1	135	Risk Ratio (M-H, Fixed, 95% CI)	2.96 [0.32, 27.71]
38.17 Duration of treatment > 1 week	5	503	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.30, 1.07]
38.18 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	5	885	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.31, 1.00]
38.19 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	2	177	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.19, 2.88]
38.20 Iron supplementation > 2 mg/kg in neither group	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.52]
38.21 PUFA >= 400 mg/100 ml milk	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.52]
39 Retinal detachment among surviving infants	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
39.1 All infants in all studies	3	432	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
39.2 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
39.3 Enteral hypertonic formulation at pharmacologic doses	1	101	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
39.4 Parenteral with or without enteral	2	331	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
39.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	331	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
39.6 Excluding intravenous vitamin E supplementation	3	432	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
39.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	432	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
39.8 Serum tocopherol level in the treatment group <= 3.5 mg/dl	3	432	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
39.9 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	432	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
39.10 Duration of treatment <= 1 week (7 days)	1	135	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
39.11 Duration of treatment > 1 week	2	297	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]
39.12 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	297	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.09]

39.13 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
40 Retinal detachment among surviving very low birth weight infants	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
40.1 All infants in all studies	3	321	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.2 Birth weight <= 1500 grams	2	236	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
40.3 Birth weight <= 1000 grams	2	134	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.4 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
40.5 Enteral hypertonic formulation at pharmacologic doses	1	101	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
40.6 Parenteral with or without enteral	2	220	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.7 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	220	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.8 Excluding intravenous vitamin E supplementation	3	321	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	321	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.10 Serum tocopherol level in the treatment group <= 3.5 mg/dl	3	321	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	321	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.12 Duration of treatment <= 1 week	1	135	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
40.13 Duration of treatment > 1 week	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.84]
40.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
41 Cicatricial retrolental fibroplasia, any stage, among patients examined after discharge	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
41.1 All infants in all studies	5	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.52, 1.27]
41.2 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.13, 1.09]
41.3 Enteral hypertonic formulation at pharmacologic doses	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.13, 1.09]

41.4 Parenteral with or without enteral	4	951	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.62]
41.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	951	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.62]
41.6 Intravenous (with or without other routes of administration)	2	778	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.55, 2.22]
41.7 Excluding intravenous vitamin E supplementation	3	274	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.37, 1.16]
41.8 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.14, 2.01]
41.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	4	953	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.54, 1.39]
41.10 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	297	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.25, 1.44]
41.11 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	755	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.55, 1.53]
41.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	5	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.52, 1.27]
41.13 Duration of treatment > 1 week	4	470	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.43, 1.29]
41.14 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	4	978	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.44, 1.24]
41.15 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.49, 2.60]
42 Cicatricial retrolental fibroplasia, any stage, among very low birth weight infants examined after discharge	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
42.1 All infants in all studies	5	858	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.48, 1.15]
42.2 Birth weight <= 1500 grams	4	824	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.45, 1.12]
42.3 Birth weight <= 1000 grams	3	82	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.26, 1.19]
42.4 Enteral	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.13, 1.09]
42.5 Enteral hypertonic formulation at pharmacologic doses	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.13, 1.09]
42.6 Parenteral with or without enteral	4	757	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.55, 1.43]



42.7 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	757	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.55, 1.43]
42.8 Intravenous (with or without other routes of administration)	2	616	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.51, 1.99]
42.9 Excluding intravenous vitamin E supplementation	3	242	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.33, 1.04]
42.10 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.14, 2.01]
42.11 Total dose of vitamin E in the treatment group > 30 IU/kg/day	4	759	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.49, 1.24]
42.12 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	135	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.22, 1.26]
42.13 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	723	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.51, 1.41]
42.14 Onset of vitamin E supplementation in the treatment group within 48 hours of life	5	858	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.48, 1.15]
42.15 Duration of treatment > 1 week	4	276	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.38, 1.10]
42.16 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	4	816	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.42, 1.18]
42.17 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.42, 1.96]
43 Blindness from retrolental fibroplasia among very low birth weight infants examined	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
43.1 All infants in all studies	4	467	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.88]
43.2 Birth weight <= 1500 grams	4	467	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.88]
43.3 Birth weight <= 1000 grams	2	48	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.84]
43.4 Enteral	2	326	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.10, 1.13]
43.5 Enteral hypertonic formulation at pharmacologic dose	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.63]
43.6 Parenteral with or without enteral	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.86]
43.7 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.86]
43.8 Excluding intravenous vitamin E supplementation	4	467	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.88]

43.9 Total dose of vitamin E in the treatment group ≤ 30 IU/kg/day	2	324	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.12, 1.46]
43.10 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	143	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.63]
43.11 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	2	326	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.10, 1.13]
43.12 Serum tocopherol level in the treatment group > 3.5 mg/dl	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.86]
43.13 Onset of vitamin E supplementation in the treatment group within 48 hours of life	4	467	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.88]
43.14 Duration of treatment > 1 week	4	467	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.88]
43.15 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	3	425	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.88]
43.16 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	42	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
43.17 Iron supplementation > 2 mg/kg/day in neither group	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.52]
43.18 PUFA ≥ 400 mg/100 ml milk	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.52]
44 Necrotizing enterocolitis	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
44.1 All infants in all studies	8	1443	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.96, 1.95]
44.2 Enteral	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
44.3 Parenteral with or without enteral	7	1413	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.94, 1.93]
44.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	1105	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.89, 1.86]
44.5 Intravenous (with or without other routes of supplementation)	2	832	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.95, 2.19]
44.6 Excluding intravenous vitamin E supplementation	6	611	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.59, 2.35]
44.7 Total dose of vitamin E in the treatment group ≤ 30 IU/kg/day	4	434	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.66, 3.88]
44.8 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	979	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.88, 1.93]
44.9 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	5	625	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.65, 3.81]

44.10 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	818	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.90, 1.95]
44.11 Onset of vitamin E supplementation in the treatment group within 48 hours of life	7	1413	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.94, 1.93]
44.12 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
44.13 Duration of treatment <= 1 week	2	279	Risk Ratio (M-H, Fixed, 95% CI)	6.88 [0.36, 131.68]
44.14 Duration of treatment > 1 week	5	619	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.53, 1.83]
44.15 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	7	1296	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.03, 2.16]
44.16 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.13, 1.95]
44.17 Iron supplementation > 2 mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
45 Necrotizing enterocolitis among very low birth weight infants	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
45.1 All infants in all studies	6	962	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.90, 1.87]
45.2 Birth weight <= 1500 grams	4	730	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.99, 2.22]
45.3 Birth weight <= 1000 grams	2	232	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.23, 1.62]
45.4 Enteral	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
45.5 Parenteral with or without enteral	5	932	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.88, 1.85]
45.6 Parenteral with hypertonic enteral formulation at pharmacologic dose	4	903	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.88, 1.85]
45.7 Intravenous (with or without other routes of supplementation)	2	630	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.94, 2.19]
45.8 Excluding intravenous vitamin E supplementation	4	332	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.46, 2.01]
45.9 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	155	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.46, 3.17]
45.10 Total dose of vitamin E in the treatment group > 30 IU/kg/day	3	777	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.86, 1.92]
45.11 Serum tocopherol level in the treatment group <= 3.5 mg/dl	3	144	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.34, 3.29]

45.12 Serum tocopherol level in the treatment group > 3.5 mg/dl	3	818	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.90, 1.95]
45.13 Onset of vitamin E supplementation in the treatment group within 48 hours of life	5	932	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.88, 1.85]
45.14 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
45.15 Duration of treatment > 1 week	5	417	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.48, 1.76]
45.16 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	5	815	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.96, 2.08]
45.17 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.13, 1.95]
45.18 Iron supplementation > 2 mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
46 Necrotizing enterocolitis among very low birth weight infants treated for > 1 week	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
46.1 All infants in all studies	5	734	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.99, 2.30]
46.2 Birth weight <= 1500 grams	4	649	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.04, 2.51]
46.3 Birth weight <= 1000 grams	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.18, 3.23]
46.4 Enteral	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
46.5 Parenteral with or without enteral	4	704	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.97, 2.28]
46.6 Parenteral with hypertonic enteral formulation at pharmacologic dose	2	549	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.97, 2.51]
46.7 Intravenous (with or without other routes of supplementation)	2	549	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.97, 2.51]
46.8 Excluding intravenous vitamin E supplementation	3	185	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.53, 3.32]
46.9 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	155	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.46, 3.17]
46.10 Total dose of vitamin E in the treatment group > 30 IU/kg/day	2	549	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.97, 2.51]
46.11 Serum tocopherol level in the treatment group <= 3.5 mg/dl	3	144	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.34, 3.29]
46.12 Serum tocopherol level in the treatment group > 3.5 mg/dl	2	590	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.02, 2.52]

46.13 Onset of vitamin E supplementation in the treatment group within 48 hours of life	4	704	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.97, 2.28]
46.14 Onset of treatment after 48 hours of life	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
46.15 Duration of treatment > 1 week	4	270	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.53, 2.43]
46.16 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	5	734	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.99, 2.30]
46.17 Iron supplementation > 2 mg/kg/day in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
47 Necrotizing enterocolitis among survivors	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
47.1 All infants in all studies	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.2 Birth weight <= 1500 grams	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.3 Parenteral with or without enteral	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.4 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.5 Excluding intravenous vitamin E supplementation	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.6 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	51	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
47.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.8 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.9 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.10 Duration of treatment <= 1 week	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.11 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	1	51	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
47.12 Total dose of vitamin E in the control group > 10 mg vit E/100 kcal	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
47.13 Iron supplementation > 2 mg/kg/day in both groups	1	51	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
48 Necrotizing enterocolitis among surviving very low birth weight infants	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

48.1 All infants in all studies	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.65]
49 Serum bilirubin concentration (mg/100 ml) on day 3-5	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
49.1 All infants in all studies	3	98	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.17, 0.57]
49.2 Birth weight >= 1000 grams	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.86 [-2.46, 0.74]
49.3 Enteral	2	58	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-1.10, 0.96]
49.4 Parenteral with or without enteral	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.86 [-2.46, 0.74]
49.5 Excluding intravenous	3	98	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.17, 0.57]
49.6 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	70	Mean Difference (IV, Fixed, 95% CI)	0.50 [-0.66, 1.66]
49.7 Total dose of vitamin E in the treatment group > 30 IU/kg/day	1	28	Mean Difference (IV, Fixed, 95% CI)	Not estimable
49.8 Serum tocopherol level in the treatment group <= 3.5 mg/dl	3	98	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.17, 0.57]
49.9 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	98	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.17, 0.57]
49.10 Duration of treatment <= 1 week	3	98	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.17, 0.57]
49.11 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	3	98	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.17, 0.57]
49.12 Iron supplementation > 2 mg/kg in neither group	2	70	Mean Difference (IV, Fixed, 95% CI)	0.50 [-0.66, 1.66]
50 Serum bilirubin concentration in very low birth weight infants	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
50.1 All infants in all studies	2	48	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.58, -0.33]
50.2 Enteral	1	28	Mean Difference (IV, Fixed, 95% CI)	Not estimable
50.3 Parenteral with or without enteral	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.93 [-4.20, 0.34]
50.4 Excluding intravenous	2	48	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.58, -0.33]
50.5 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.93 [-4.20, 0.34]
50.6 Total dose of vitamin E in the treatment group > 30 IU/kg/day	1	28	Mean Difference (IV, Fixed, 95% CI)	Not estimable
50.7 Serum tocopherol level in the treatment group <= 3.5 mg/g	2	48	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.58, -0.33]
50.8 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	68	Mean Difference (IV, Fixed, 95% CI)	-1.13 [-2.13, -0.12]

50.9 Duration of treatment ≤ 1 week	2	48	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.58, -0.33]
50.10 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	2	48	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.58, -0.33]
50.11 Iron supplementation > 2 mg/kg in neither group	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.93 [-4.20, 0.34]
51 Serum bilirubin concentration on day 3-5 in a specific group (no hemolysis, polycythemia, prior transfus	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
51.1 All infants in all studies	1	62	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.20, 2.40]
52 Hemoglobin concentration (g/ 100 ml)	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
52.1 All infants in all studies	8	416	Mean Difference (IV, Fixed, 95% CI)	0.46 [0.24, 0.69]
52.2 Birth weight > 1000 grams	2	162	Mean Difference (IV, Fixed, 95% CI)	0.49 [0.20, 0.77]
52.3 Enteral	7	396	Mean Difference (IV, Fixed, 95% CI)	0.48 [0.25, 0.71]
52.4 Parenteral with or without enteral	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.21, 1.21]
52.5 Excluding intravenous vitamin E supplementation	8	416	Mean Difference (IV, Fixed, 95% CI)	0.46 [0.24, 0.69]
52.6 Total dose of vitamin E in the treatment group ≤ 30 IU/kg/day	5	338	Mean Difference (IV, Fixed, 95% CI)	0.52 [0.29, 0.76]
52.7 Total dose of vitamin E in the treatment group >30 IU/ kg/day	2	48	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-1.84, 0.30]
52.8 Serum tocopherol level in the treatment group ≤ 3.5 mg/dl	6	356	Mean Difference (IV, Fixed, 95% CI)	0.47 [0.23, 0.71]
52.9 Onset of vitamin E supplementation in the treatment group within 48 hours of life	4	285	Mean Difference (IV, Fixed, 95% CI)	0.48 [0.21, 0.75]
52.10 Onset of vitamin E supplementation in the treatment group after 48 hours of life	4	131	Mean Difference (IV, Fixed, 95% CI)	0.44 [0.02, 0.85]
52.11 Duration of treatment ≤ 1 week	3	78	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-1.44, 0.33]
52.12 Duration of treatment > 1 week	5	338	Mean Difference (IV, Fixed, 95% CI)	0.54 [0.30, 0.77]
52.13 Total dose of vitamin E in the control group ≤ 10 mg vit E/100 kcal	8	416	Mean Difference (IV, Fixed, 95% CI)	0.46 [0.24, 0.69]
52.14 Iron supplementation in both groups	4	161	Mean Difference (IV, Fixed, 95% CI)	0.57 [0.24, 0.91]
52.15 Iron supplementation in neither group	5	227	Mean Difference (IV, Fixed, 95% CI)	0.47 [0.16, 0.78]

52.16 PUFA >= 400 mg/100 ml milk	1	90	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.02, 0.42]
53 Hemoglobin concentration in very low birth weight infants	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
53.1 All infants in all studies	4	196	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.09, 0.77]
53.2 Enteral	4	196	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.09, 0.77]
53.3 Excluding intravenous vitamin E supplementation	4	196	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.09, 0.77]
53.4 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	138	Mean Difference (IV, Fixed, 95% CI)	0.53 [0.16, 0.90]
53.5 Total dose of vitamin E in the treatment group >30 IU/kg/day	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.92, 0.52]
53.6 Serum tocopherol level in the treatment group <= 3.5 mg/dl	4	196	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.09, 0.77]
53.7 Onset of vitamin E supplementation in the treatment group within 48 hours of life	3	166	Mean Difference (IV, Fixed, 95% CI)	0.42 [0.07, 0.78]
53.8 Onset of vitamin E supplementation in the treatment group after 48 hours of life	1	30	Mean Difference (IV, Fixed, 95% CI)	0.57 [-0.70, 1.84]
53.9 Duration of treatment <= 1 week	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.92, 0.52]
53.10 Duration of treatment > 1 week	3	168	Mean Difference (IV, Fixed, 95% CI)	0.53 [0.17, 0.89]
53.11 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	4	196	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.09, 0.77]
53.12 Iron supplementation in both groups	2	100	Mean Difference (IV, Fixed, 95% CI)	0.67 [0.23, 1.10]
53.13 Iron supplementation in neither group	2	157	Mean Difference (IV, Fixed, 95% CI)	0.51 [0.17, 0.86]
53.14 PUFA >= 400 mg/100 ml milk	1	90	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.02, 0.42]
54 Reticulocyte count (%)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
54.1 All infants in all studies	2	201	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.24, -1.07]
54.2 Enteral	2	201	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.24, -1.07]
54.3 Excluding intravenous vitamin E supplementation	2	201	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.24, -1.07]
54.4 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	201	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.24, -1.07]
54.5 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	201	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.24, -1.07]



54.6 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	201	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.24, -1.07]
54.7 Duration of treatment > 1 week	2	201	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.24, -1.07]
54.8 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	201	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-2.24, -1.07]
54.9 Iron supplementation in both groups	1	70	Mean Difference (IV, Fixed, 95% CI)	-1.96 [-2.89, -1.03]
54.10 Iron supplementation in neither group	2	131	Mean Difference (IV, Fixed, 95% CI)	-1.47 [-2.22, -0.72]
54.11 PUFA >= 400 mg/100 ml milk	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.50, 0.90]
55 Reticulocyte count (%) in very low birth weight infants	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
55.1 All infants in all studies	1	64	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.50, 0.90]
56 Reticulocyte count (million per liter)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
56.1 All infants in all studies	2	71	Mean Difference (IV, Fixed, 95% CI)	-34.02 [-46.19, -21.84]
56.2 Enteral	2	71	Mean Difference (IV, Fixed, 95% CI)	-34.02 [-46.19, -21.84]
56.3 Excluding intravenous vitamin E supplementation	2	71	Mean Difference (IV, Fixed, 95% CI)	-34.02 [-46.19, -21.84]
56.4 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	41	Mean Difference (IV, Fixed, 95% CI)	-9.20 [-27.36, 8.96]
56.5 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	71	Mean Difference (IV, Fixed, 95% CI)	-34.02 [-46.19, -21.84]
56.6 Onset of vitamin E supplementation in the treatment group after 48 hours of life	2	71	Mean Difference (IV, Fixed, 95% CI)	-34.02 [-46.19, -21.84]
56.7 Duration of treatment > 1 week	2	71	Mean Difference (IV, Fixed, 95% CI)	-34.02 [-46.19, -21.84]
56.8 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	71	Mean Difference (IV, Fixed, 95% CI)	-34.02 [-46.19, -21.84]
56.9 Iron supplementation in both groups	2	71	Mean Difference (IV, Fixed, 95% CI)	-34.02 [-46.19, -21.84]
57 Reticulocyte count (million per liter) in very low birth weight infants	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
57.1 All infants in all studies	1	30	Mean Difference (IV, Fixed, 95% CI)	-54.27 [-70.67, -37.87]
58 Number of transfusions	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
58.1 All infants in all studies	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.17, 0.77]

59 Number of transfusions among survivors	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
59.1 All infants in all studies	1	135	Mean Difference (IV, Fixed, 95% CI)	1.20 [-1.42, 3.82]
60 Amount of blood transfused (ml/kg) among very low birth weight infants	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
60.1 All infants in all studies	2	454	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-16.86, 15.92]
60.2 Birth weight <= 1500 grams	2	454	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-16.86, 15.92]
60.3 Enteral	1	30	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-20.91, 14.71]
60.4 Parenteral with or without enteral	1	424	Mean Difference (IV, Fixed, 95% CI)	14.0 [-27.77, 55.77]
60.5 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	424	Mean Difference (IV, Fixed, 95% CI)	14.0 [-27.77, 55.77]
60.6 Intravenous vitamin E supplementation	1	424	Mean Difference (IV, Fixed, 95% CI)	14.0 [-27.77, 55.77]
60.7 Excluding intravenous supplementation	1	30	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-20.91, 14.71]
60.8 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	30	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-20.91, 14.71]
60.9 Total dose of vitamin E in the treatment group > 30 IU/kg/day	1	424	Mean Difference (IV, Fixed, 95% CI)	14.0 [-27.77, 55.77]
60.10 Serum tocopherol level in the treatment group <= 3.5 mg/dl	1	30	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-20.91, 14.71]
60.11 Serum tocopherol level in the treatment group > 3.5 mg/dl	1	424	Mean Difference (IV, Fixed, 95% CI)	14.0 [-27.77, 55.77]
60.12 Onset of vitamin E supplementation in the treatment group within 48 hours of life	1	424	Mean Difference (IV, Fixed, 95% CI)	14.0 [-27.77, 55.77]
60.13 Onset of vitamin E supplementation in the treatment group after 48 hours of life	1	30	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-20.91, 14.71]
60.14 Duration of treatment > 1 week	1	30	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-20.91, 14.71]
60.15 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	454	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-16.86, 15.92]
60.16 Iron supplementation in both groups	1	30	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-20.91, 14.71]
61 Amount of blood transfused (ml/kg) among surviving low birth weight infants	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

61.1 All infants in all studies	1	135	Mean Difference (IV, Fixed, 95% CI)	18.10 [-17.14, 53.34]
62 Platelet count (thousands/ microliter)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
62.1 All infants in all studies	2	109	Mean Difference (IV, Fixed, 95% CI)	-29.52 [-88.81, 29.76]
62.2 Birth weight <= 1500 grams	1	68	Mean Difference (IV, Fixed, 95% CI)	-45.0 [-114.33, 24.33]
62.3 Enteral	2	109	Mean Difference (IV, Fixed, 95% CI)	-29.52 [-88.81, 29.76]
62.4 Excluding intravenous vitamin E supplementation\	2	109	Mean Difference (IV, Fixed, 95% CI)	-29.52 [-88.81, 29.76]
62.5 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	2	109	Mean Difference (IV, Fixed, 95% CI)	-29.52 [-88.81, 29.76]
62.6 Serum tocopherol level in the treatment group <= 3.5 mg/dl	2	109	Mean Difference (IV, Fixed, 95% CI)	-29.52 [-88.81, 29.76]
62.7 Onset of vitamin E supplementation in the treatment group within 48 hours of life	1	68	Mean Difference (IV, Fixed, 95% CI)	-45.0 [-114.33, 24.33]
62.8 Onset of therapy after 48 hours of life	1	41	Mean Difference (IV, Fixed, 95% CI)	12.60 [-101.78, 126.98]
62.9 Duration of treatment > 1 week	2	109	Mean Difference (IV, Fixed, 95% CI)	-29.52 [-88.81, 29.76]
62.10 Total dose of vitamin E in the control group <= 10 mg vit E/100 kcal	2	109	Mean Difference (IV, Fixed, 95% CI)	-29.52 [-88.81, 29.76]
62.11 Iron supplementation > 2 mg/kg in both groups	1	41	Mean Difference (IV, Fixed, 95% CI)	12.60 [-101.78, 126.98]
63 Prothrombin time (PT, seconds)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
63.1 All infants in all studies	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.62, 0.42]
64 Partial thromboplastin time (PTT, seconds)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
64.1 All infants in all studies	1	47	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-12.93, 6.13]
65 Fibrinogen concentration (mg/ 100 ml)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
65.1 All infants in all studies	1	47	Mean Difference (IV, Fixed, 95% CI)	49.0 [-14.47, 112.47]
66 Retinal hemorrhage among very low birth weight infants examined/surviving	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
66.1 All infants in all studies	1	232	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.97, 4.89]
66.2 Birth weight <= 1000 grams	1	85	Risk Ratio (M-H, Fixed, 95% CI)	3.58 [1.28, 10.00]
67 Reaction at site of injection	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
67.1 All infants in all studies	2	357	Risk Ratio (M-H, Fixed, 95% CI)	4.13 [0.47, 36.68]
67.2 Parenteral with or without enteral	2	357	Risk Ratio (M-H, Fixed, 95% CI)	4.13 [0.47, 36.68]

67.3 Parenteral with hypertonic enteral formulation at pharmacologic dose	1	147	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 103.77]
67.4 Excluding intravenous vitamin E supplementation	2	357	Risk Ratio (M-H, Fixed, 95% CI)	4.13 [0.47, 36.68]
67.5 Total dose of vitamin E in the treatment group <= 30 IU/kg/day	1	210	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [0.13, 77.05]
67.6 Total dose of vitamin E in the treatment group > 30 IU/kg/day	1	147	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 103.77]
67.7 Serum tocopherol level in the treatment group <= 3.5 mg/dl	1	210	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [0.13, 77.05]
67.8 Serum tocopherol level in the treatment group > 3.5 mg/dl	1	147	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 103.77]
67.9 Onset of vitamin E supplementation in the treatment group within 48 hours of life	2	357	Risk Ratio (M-H, Fixed, 95% CI)	4.13 [0.47, 36.68]
67.10 Duration of treatment <= 1 week	1	210	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [0.13, 77.05]
67.11 Duration of treatment > 1 week	1	147	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 103.77]
68 Reaction at site of injection in very low birth weight infants	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
68.1 All infants in all studies	1	147	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 103.77]
68.2 Birth weight <= 1000 grams	1	147	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [0.25, 103.77]

## Comparison 2. Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All infants	1	44	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 98.52]
2 Bronchopulmonary dysplasia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 All infants	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.31, 1.80]
3 Patent ductus arteriosus	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 All infants	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.19, 2.97]
4 Sepsis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 All infants	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.96]
5 Germinal matrix-intraventricular hemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 All infants	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.50, 2.61]
6 Stage IV (intraparenchymal) intraventricular hemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

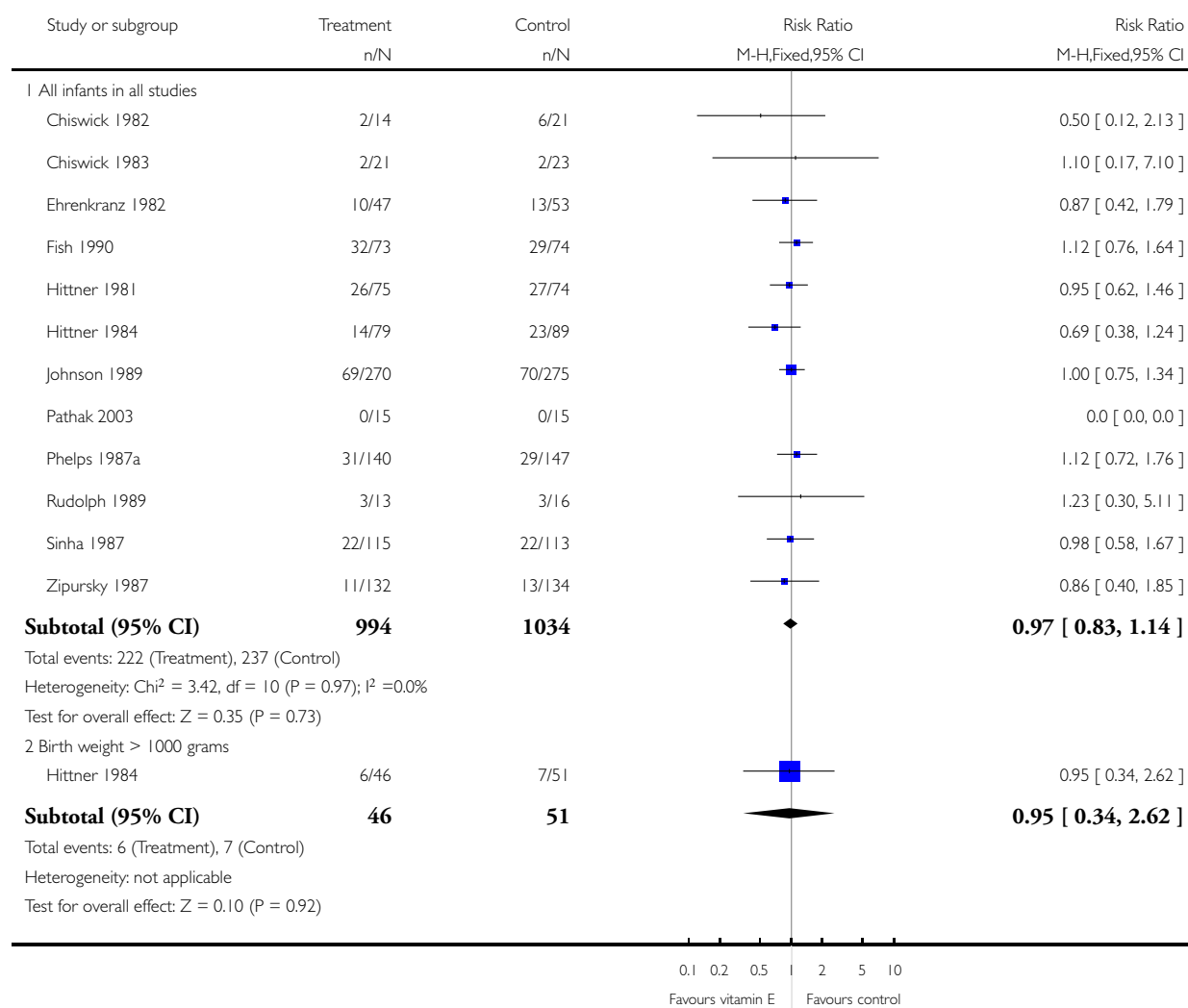
6.1 All infants	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.76]
7 Necrotizing enterocolitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 All infants	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.61]
8 Exchange transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 All infants	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.50, 1.29]

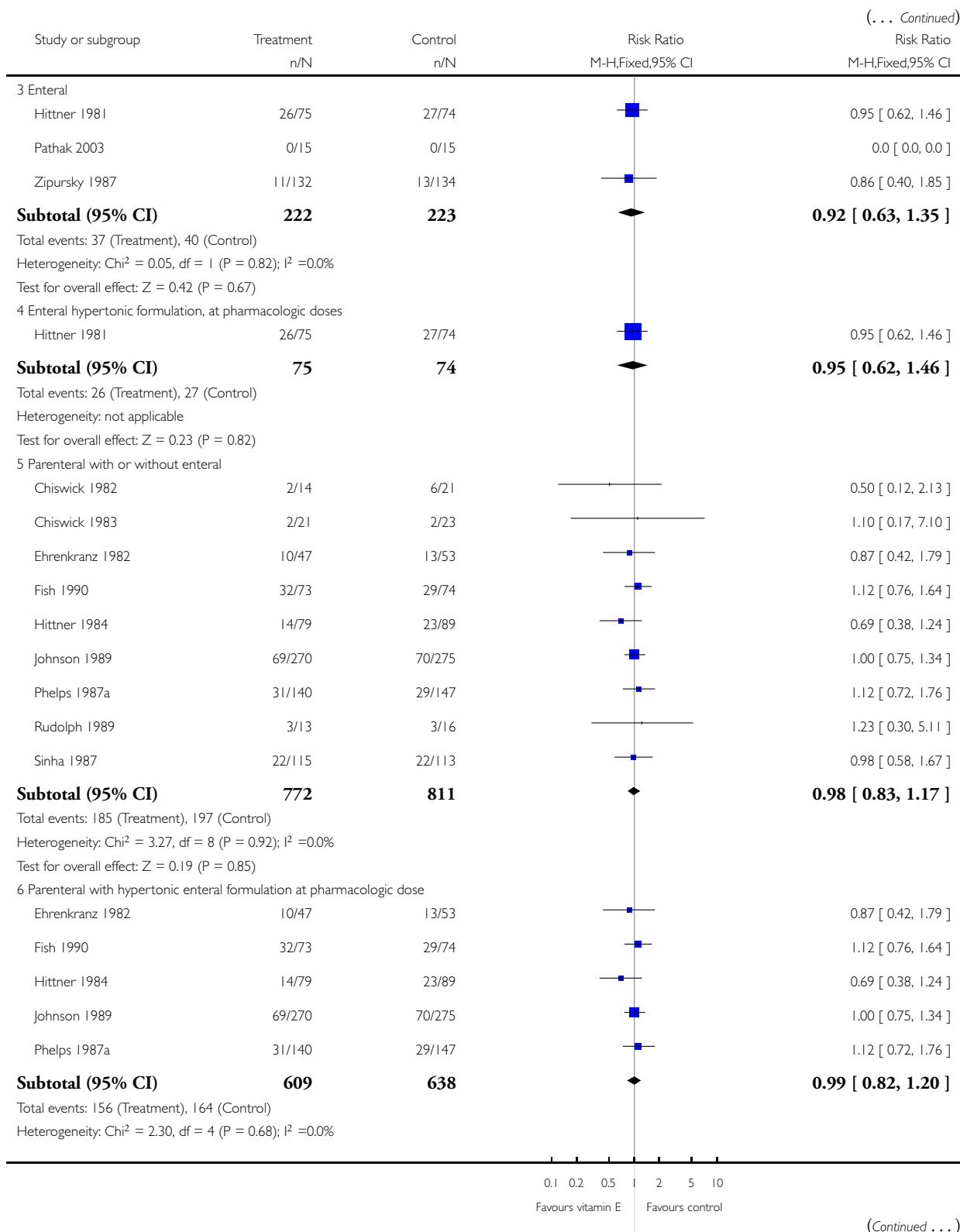
### Analysis 1.1. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 1 Mortality until discharge.

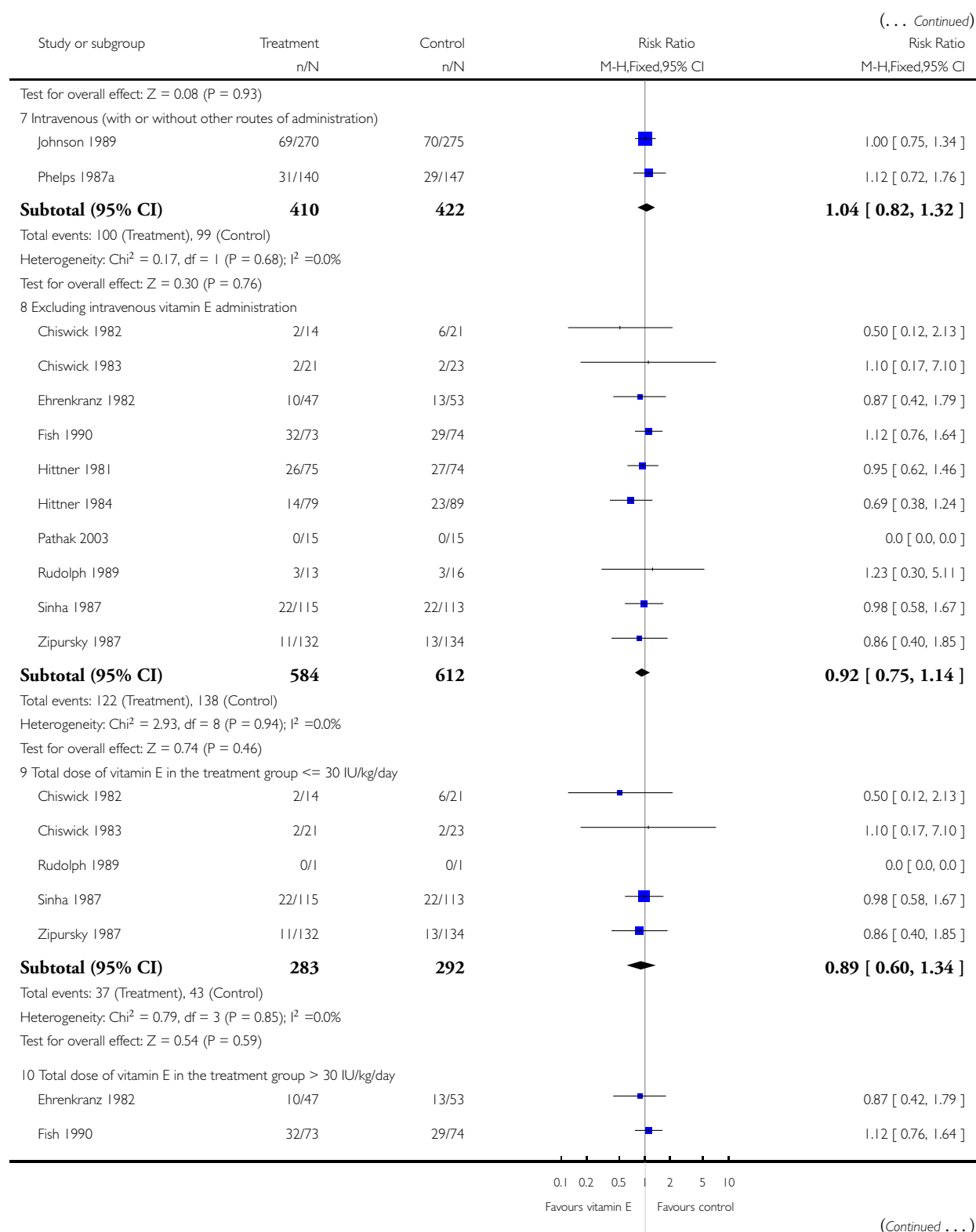
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

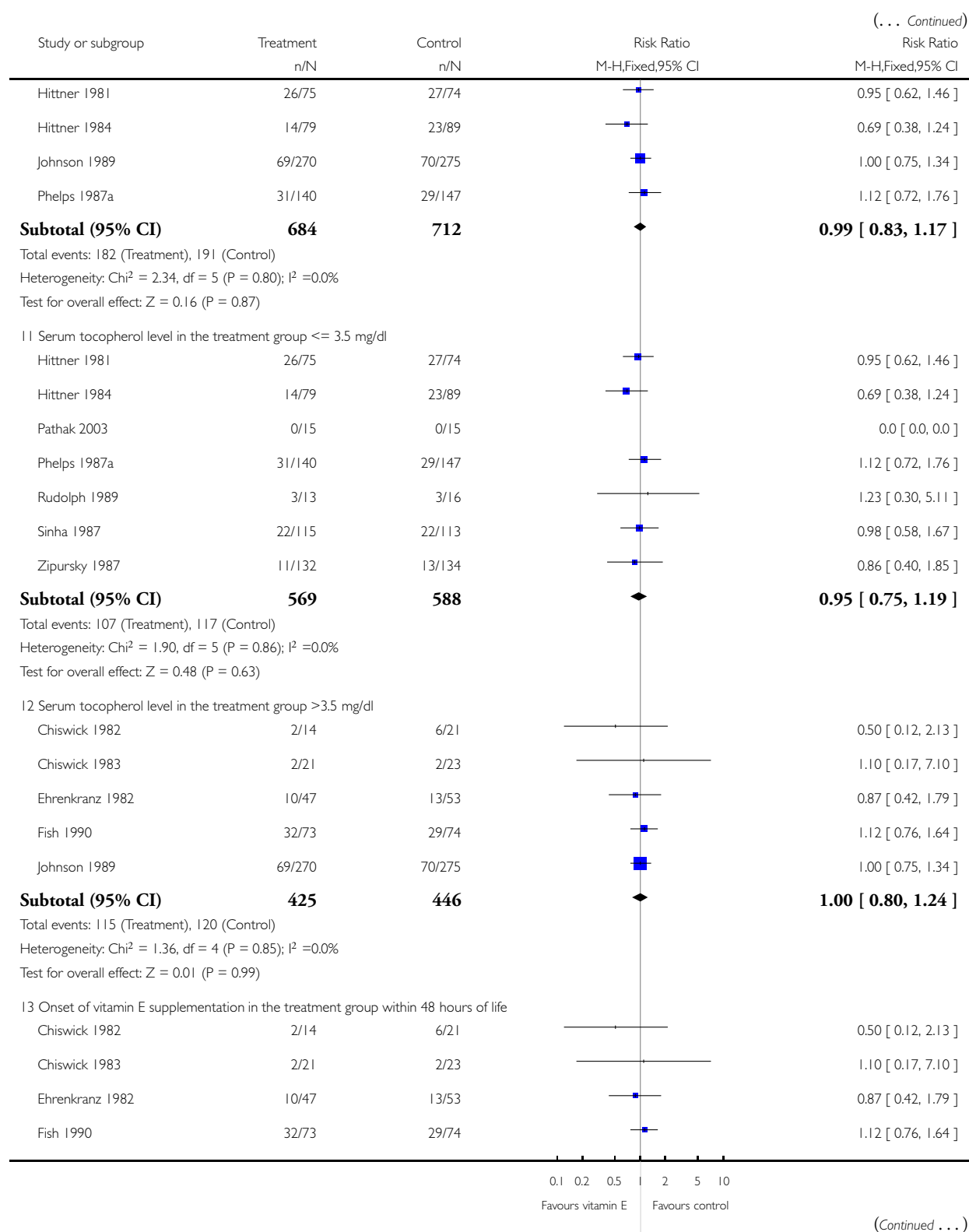
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 1 Mortality until discharge

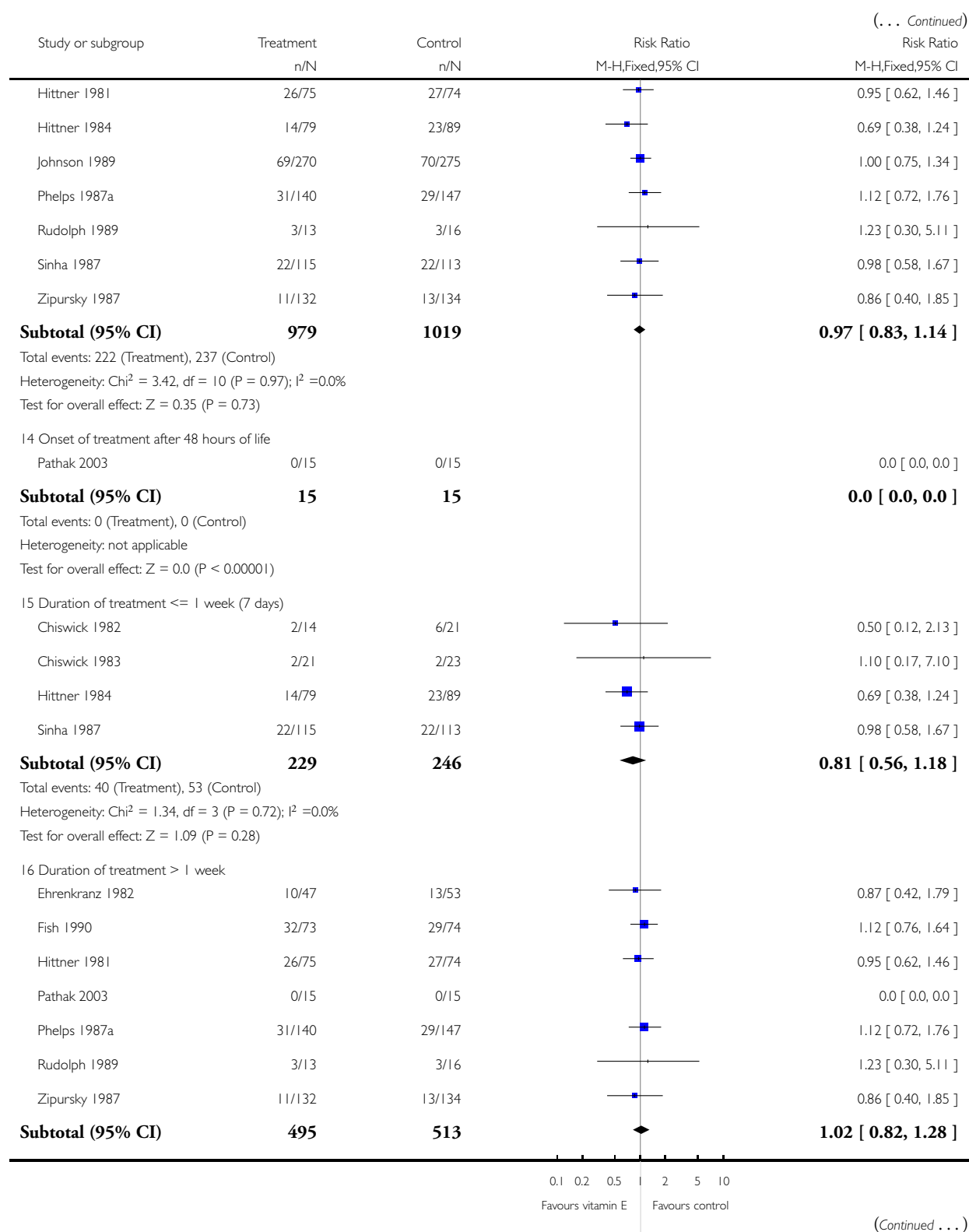


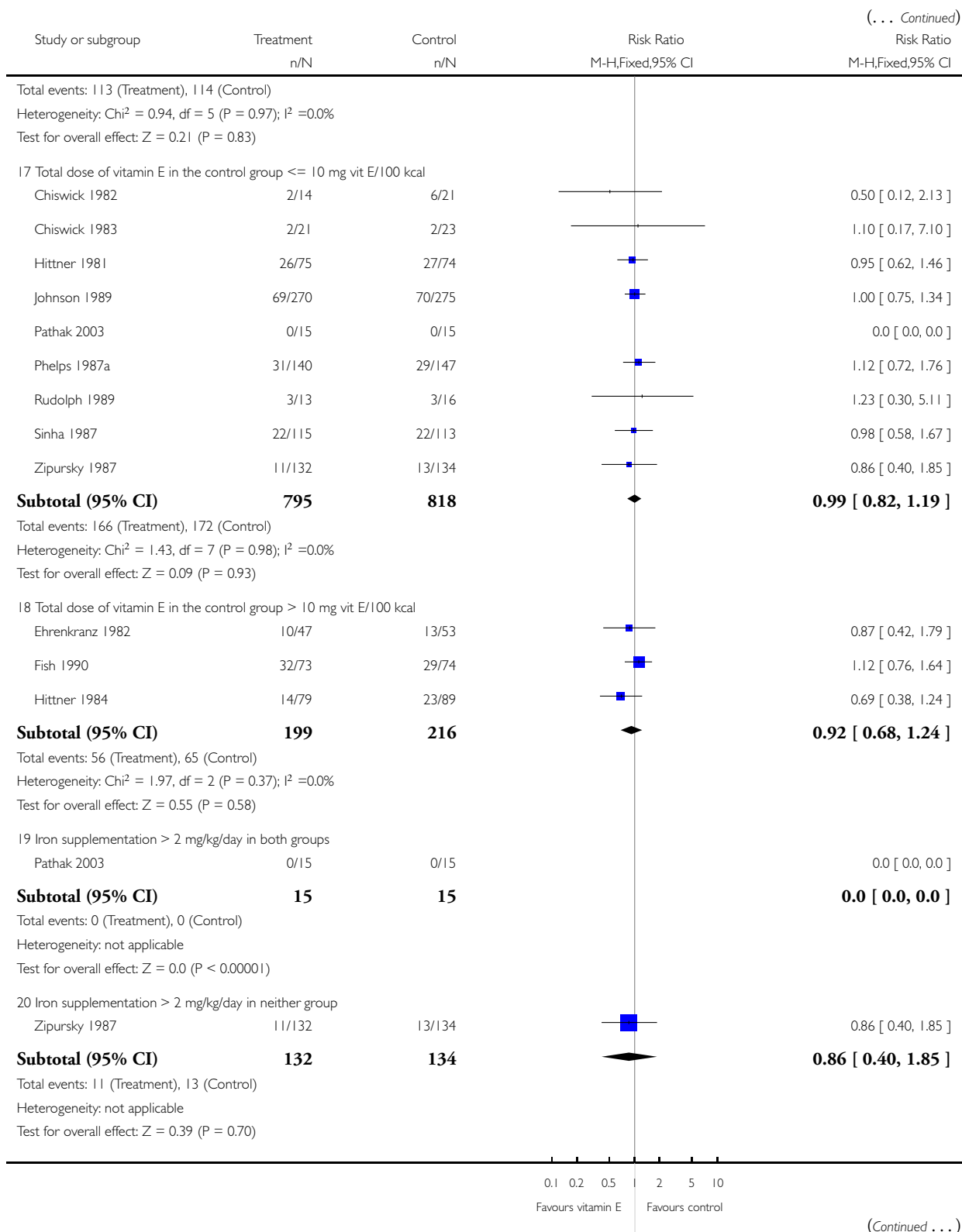


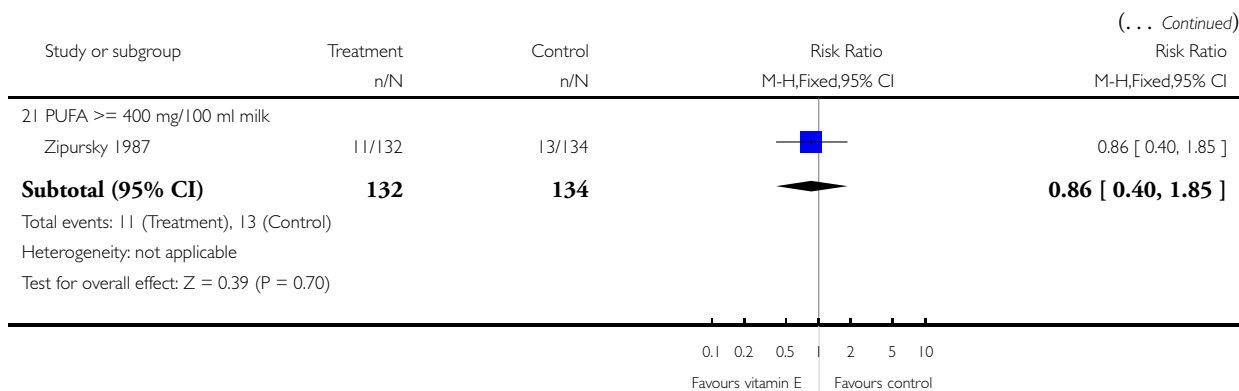










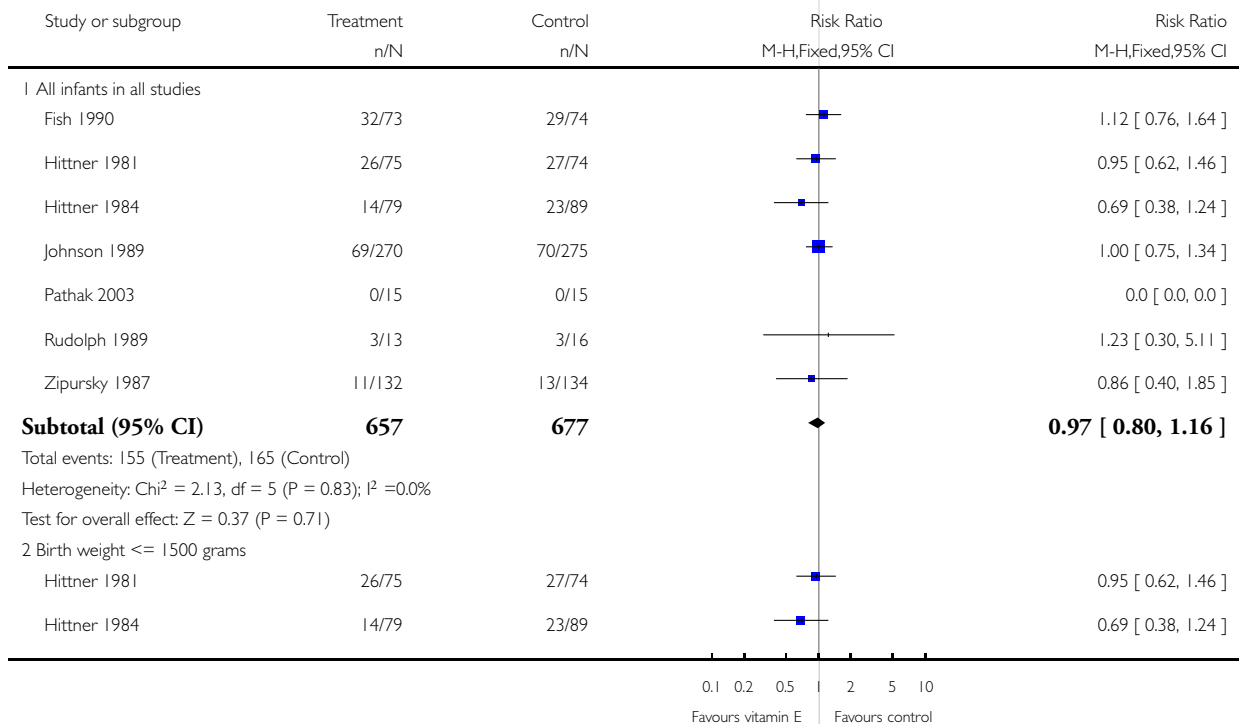


### Analysis 1.2. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 2 Mortality until discharge among very low birth weight infants.

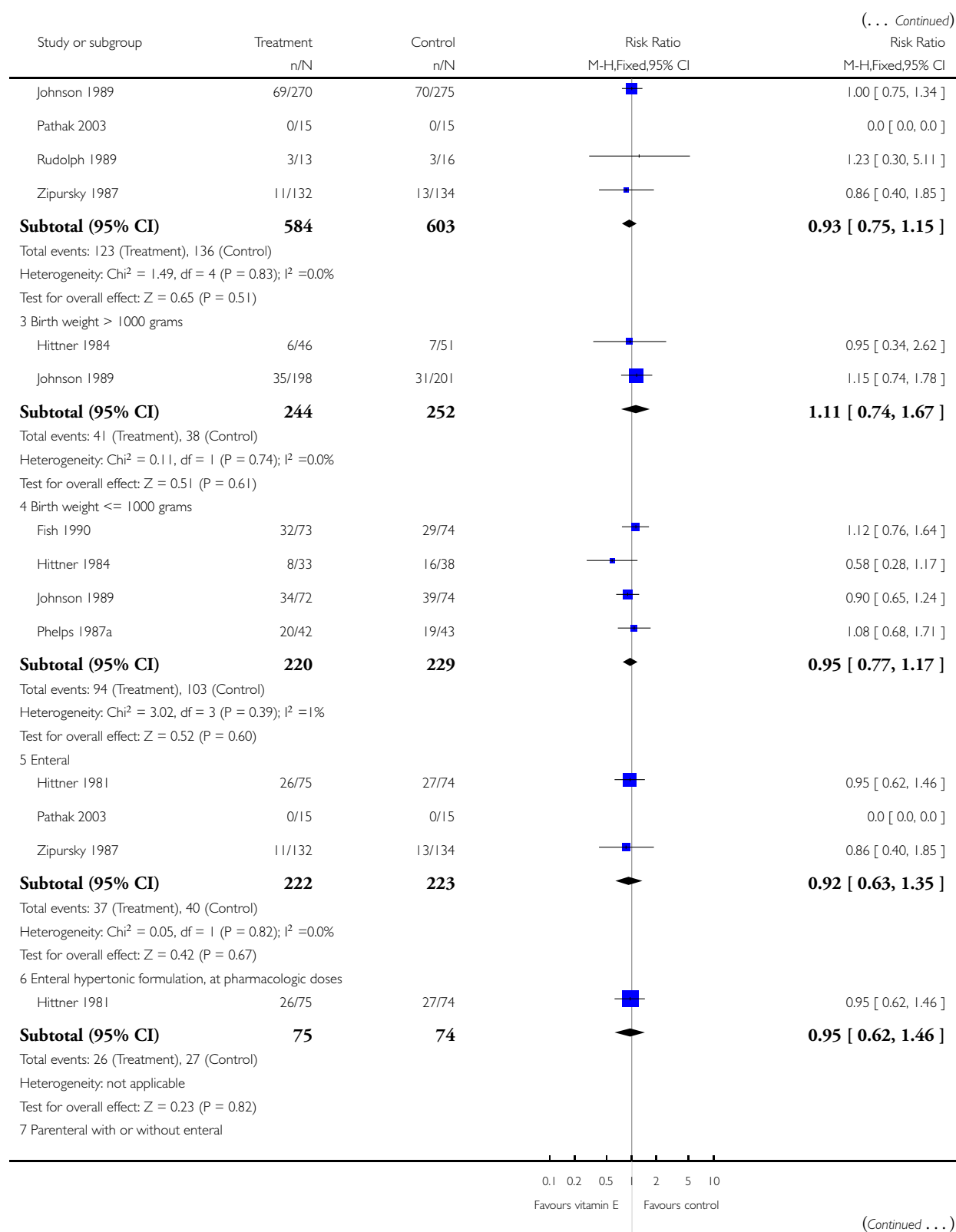
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

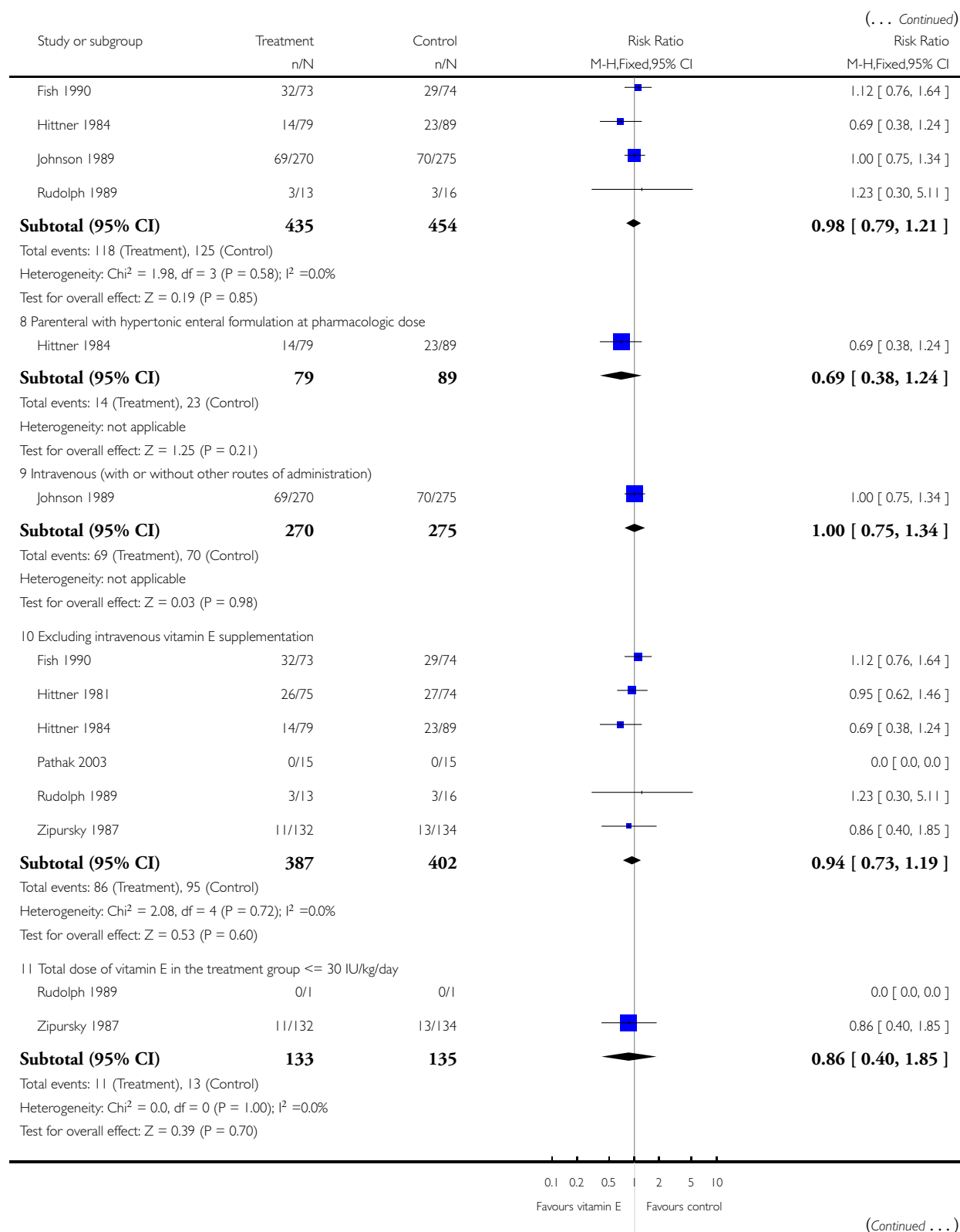
Comparison: 1 Vitamin E versus placebo or no vitamin E

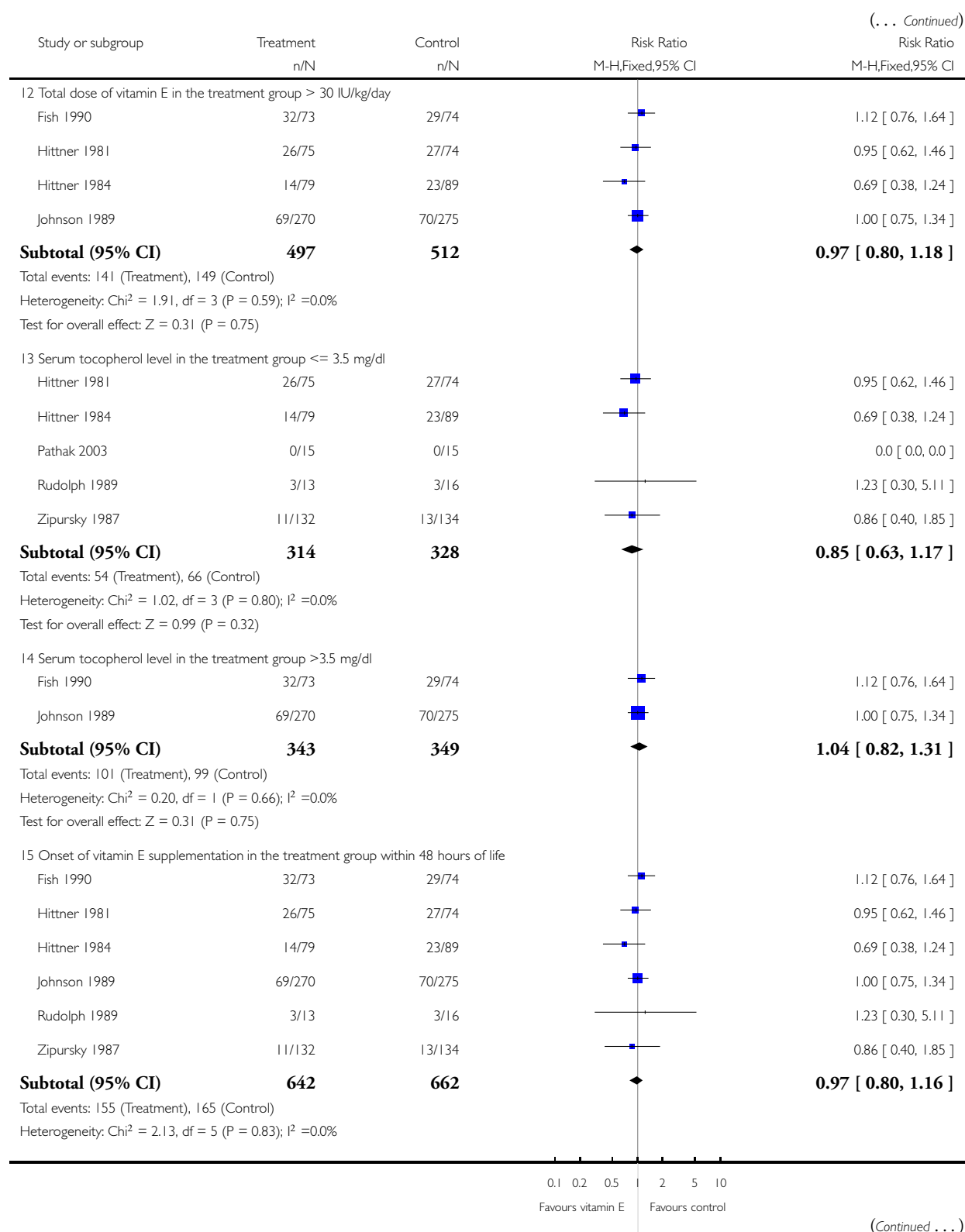
Outcome: 2 Mortality until discharge among very low birth weight infants

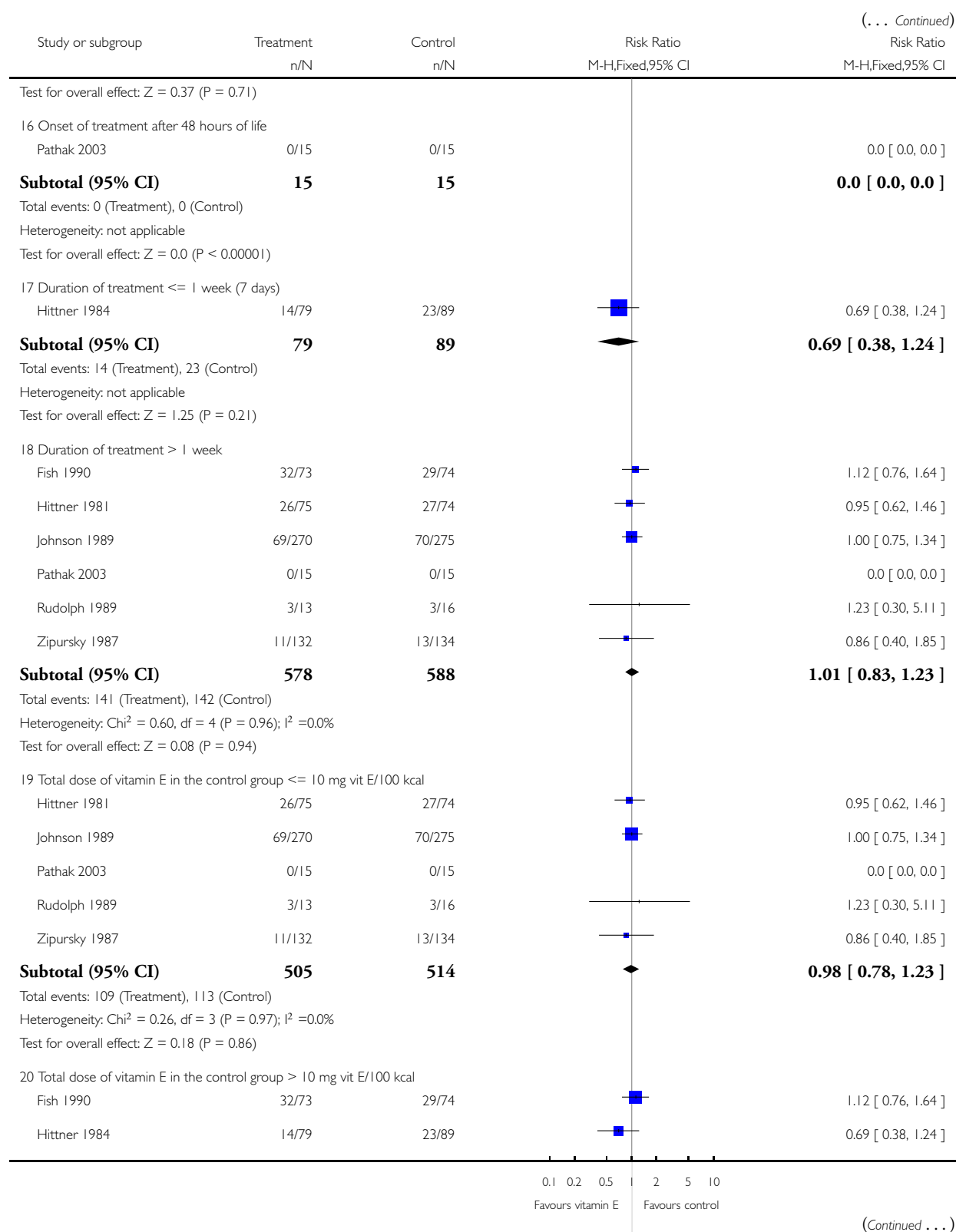


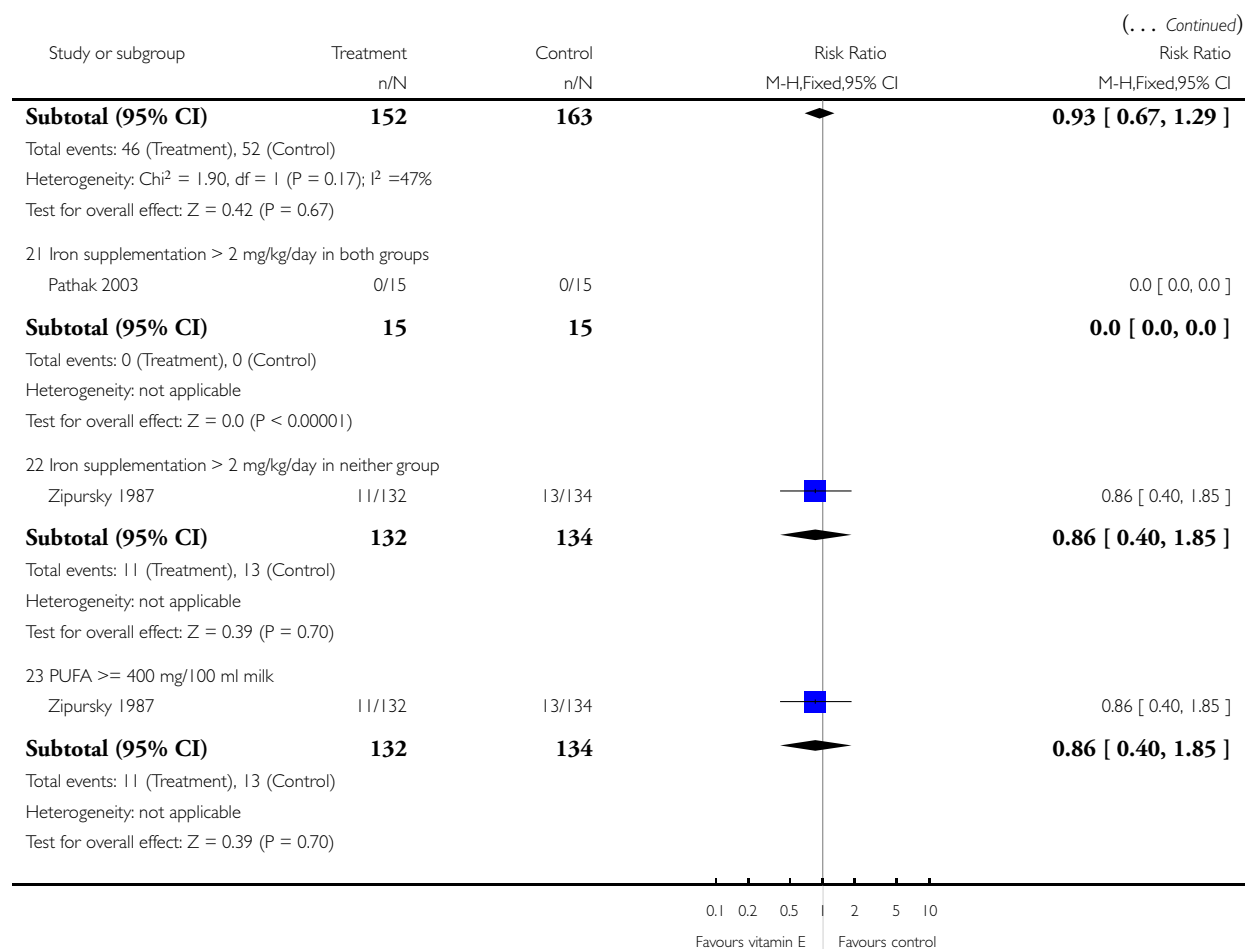
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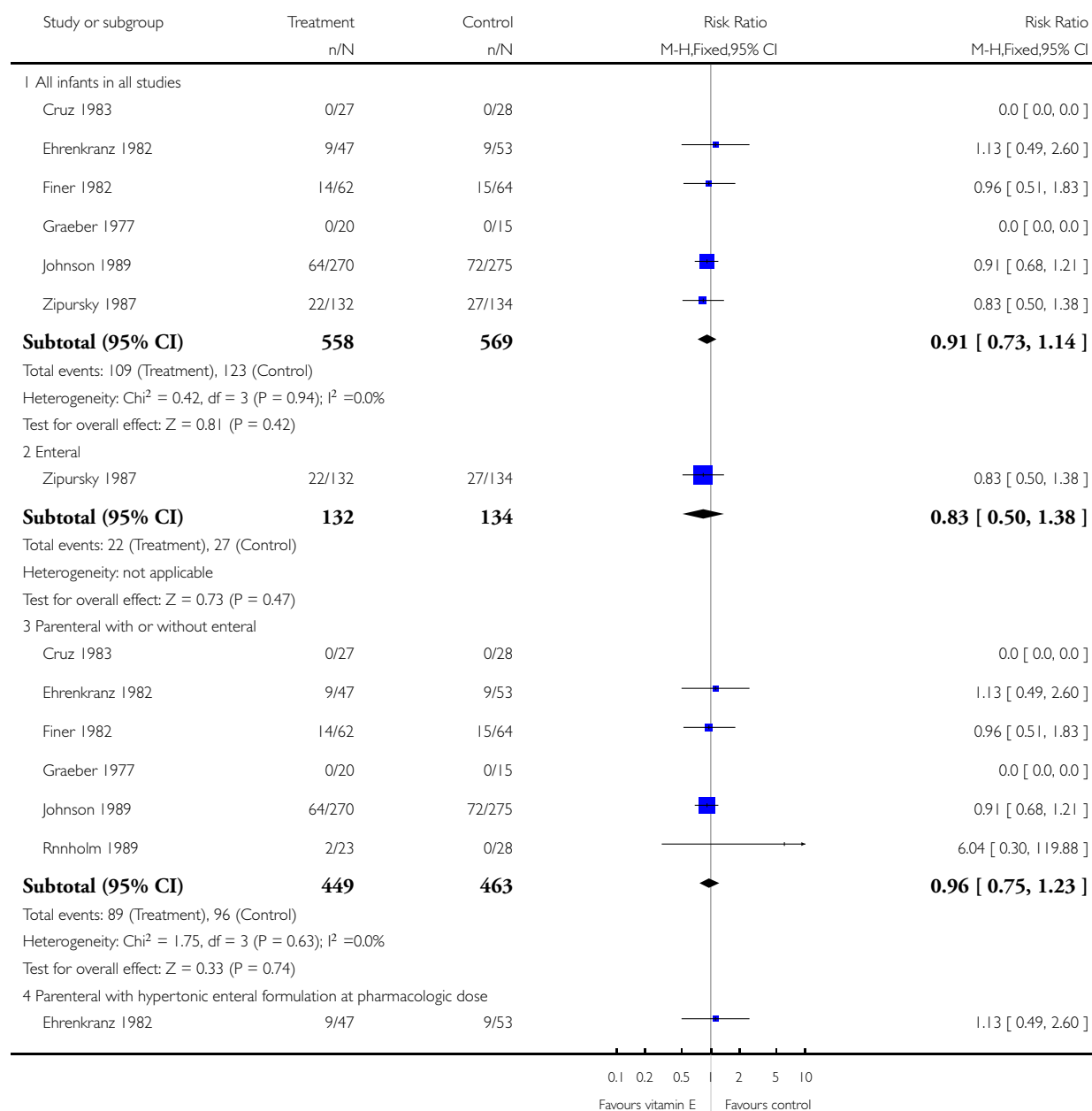


### Analysis 1.3. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 3 Bronchopulmonary dysplasia.

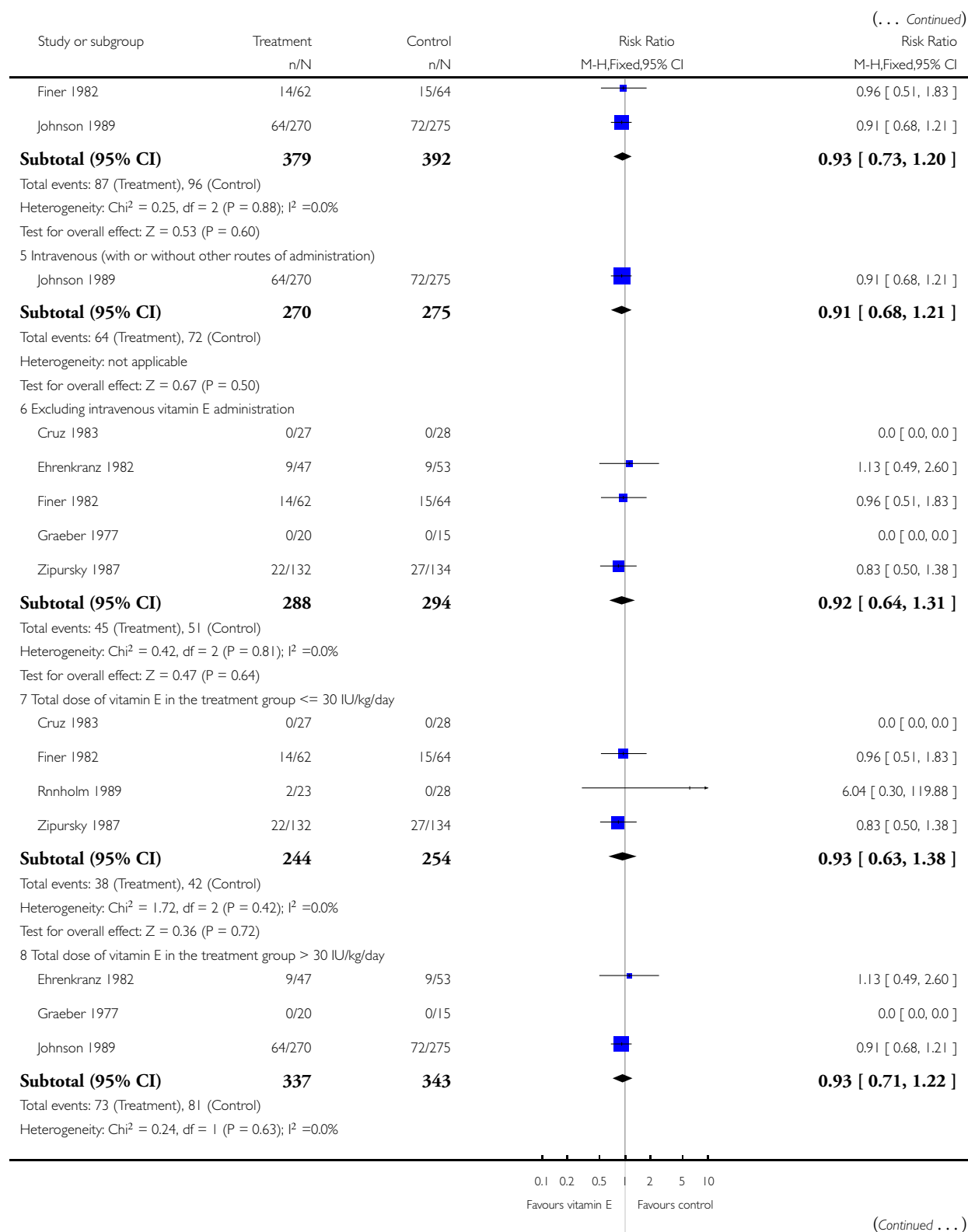
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

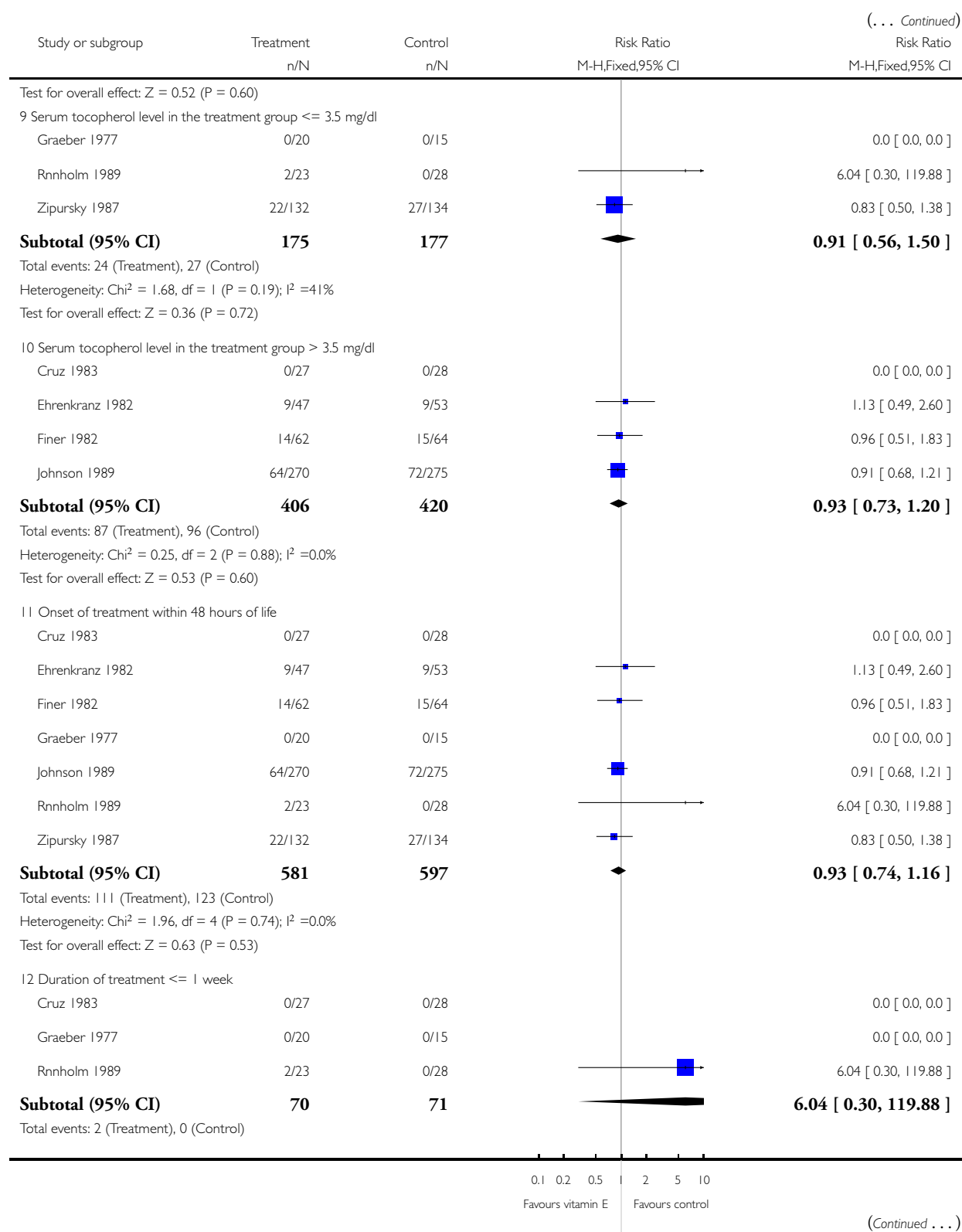
Comparison: 1 Vitamin E versus placebo or no vitamin E

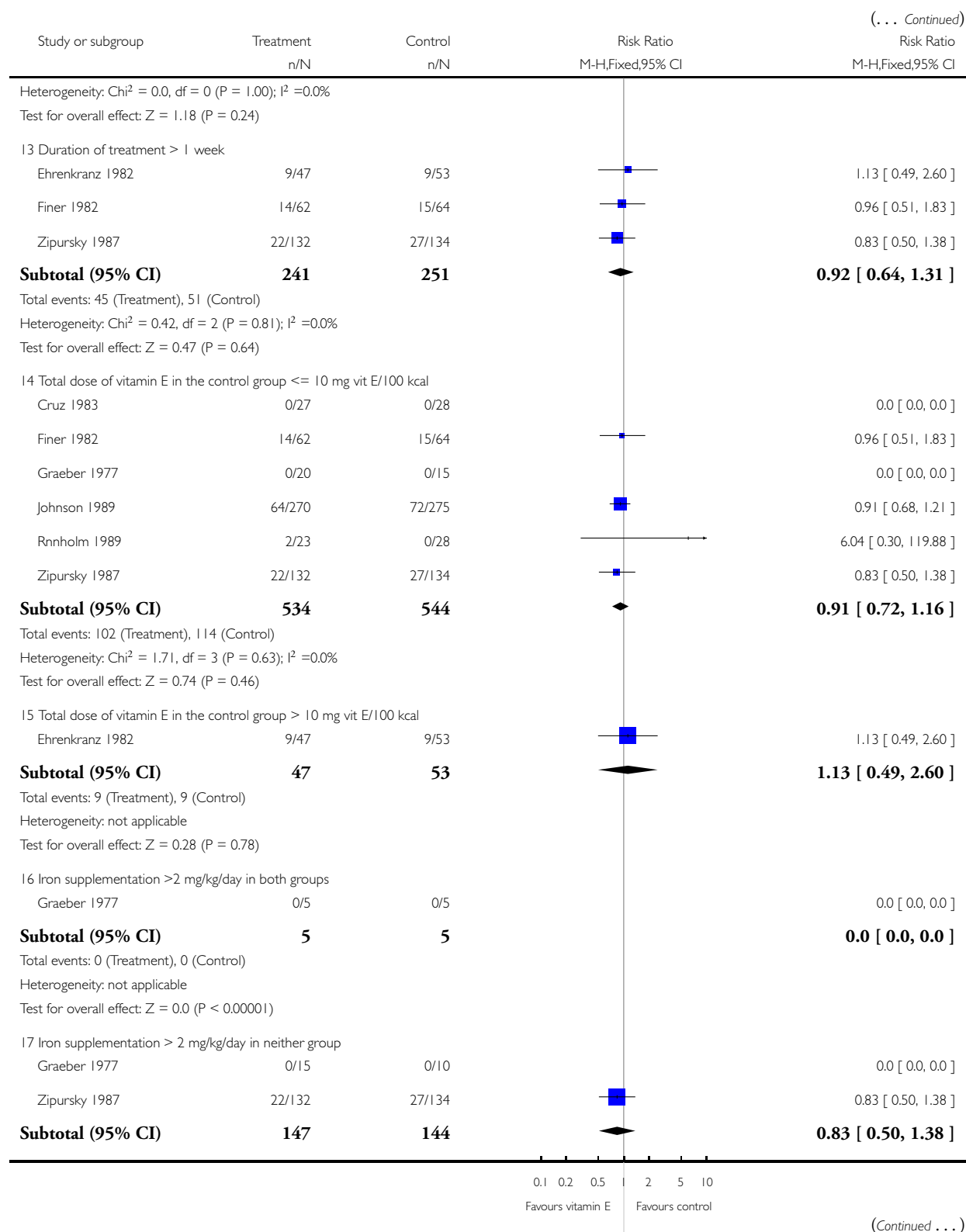
Outcome: 3 Bronchopulmonary dysplasia

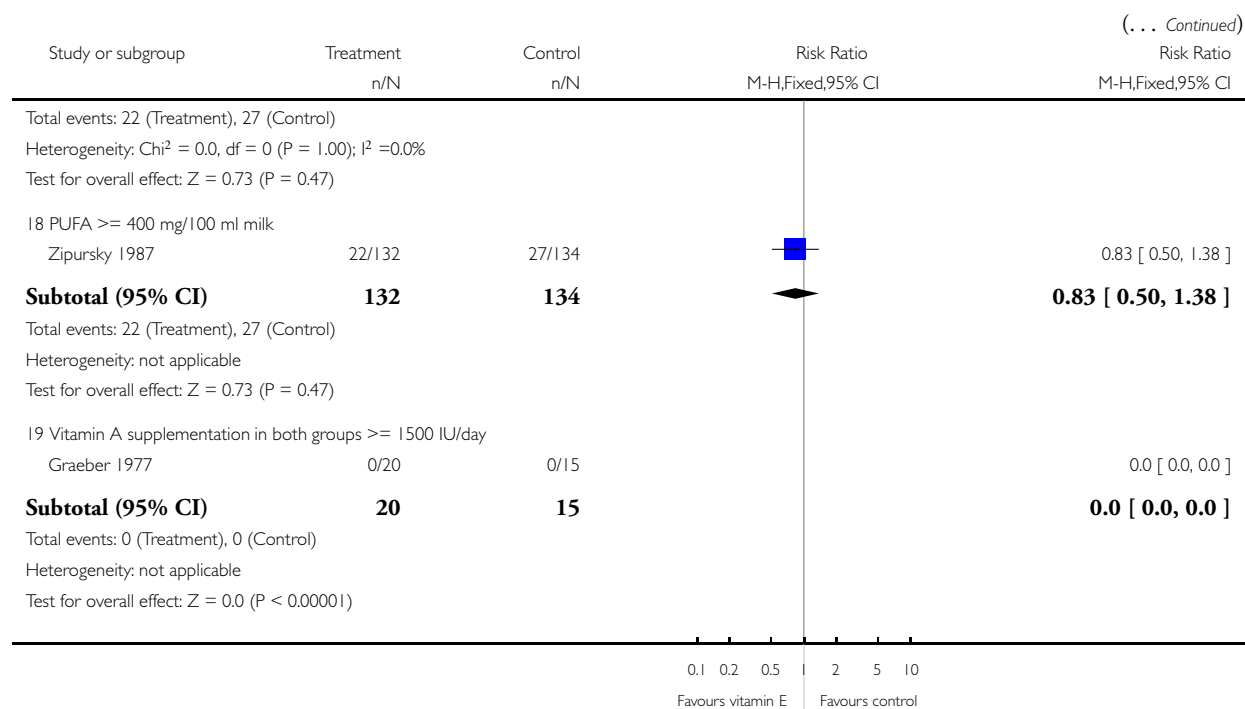


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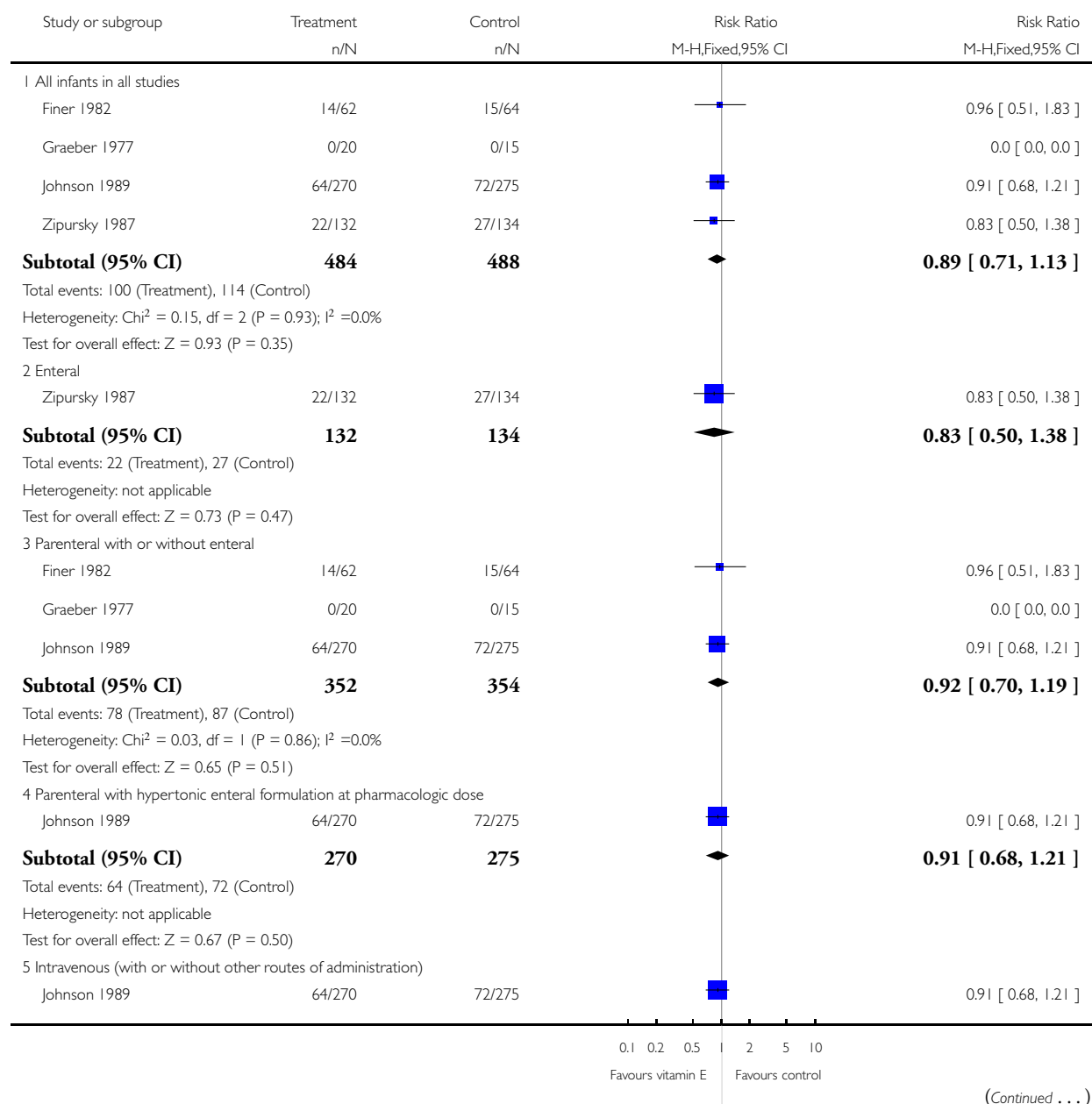


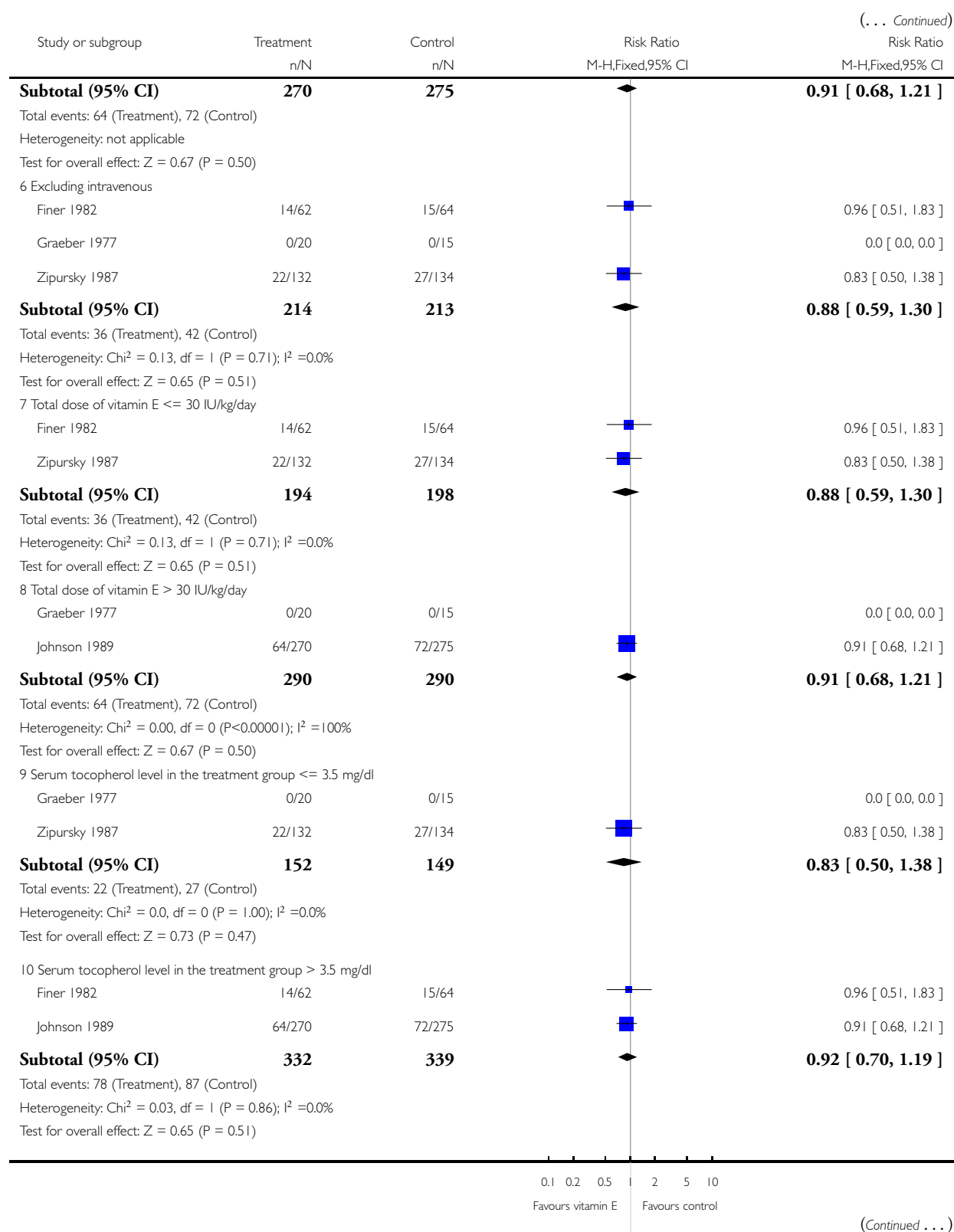
# **Analysis 1.4. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 4 Bronchopulmonary dysplasia among very low birth weight infants.**

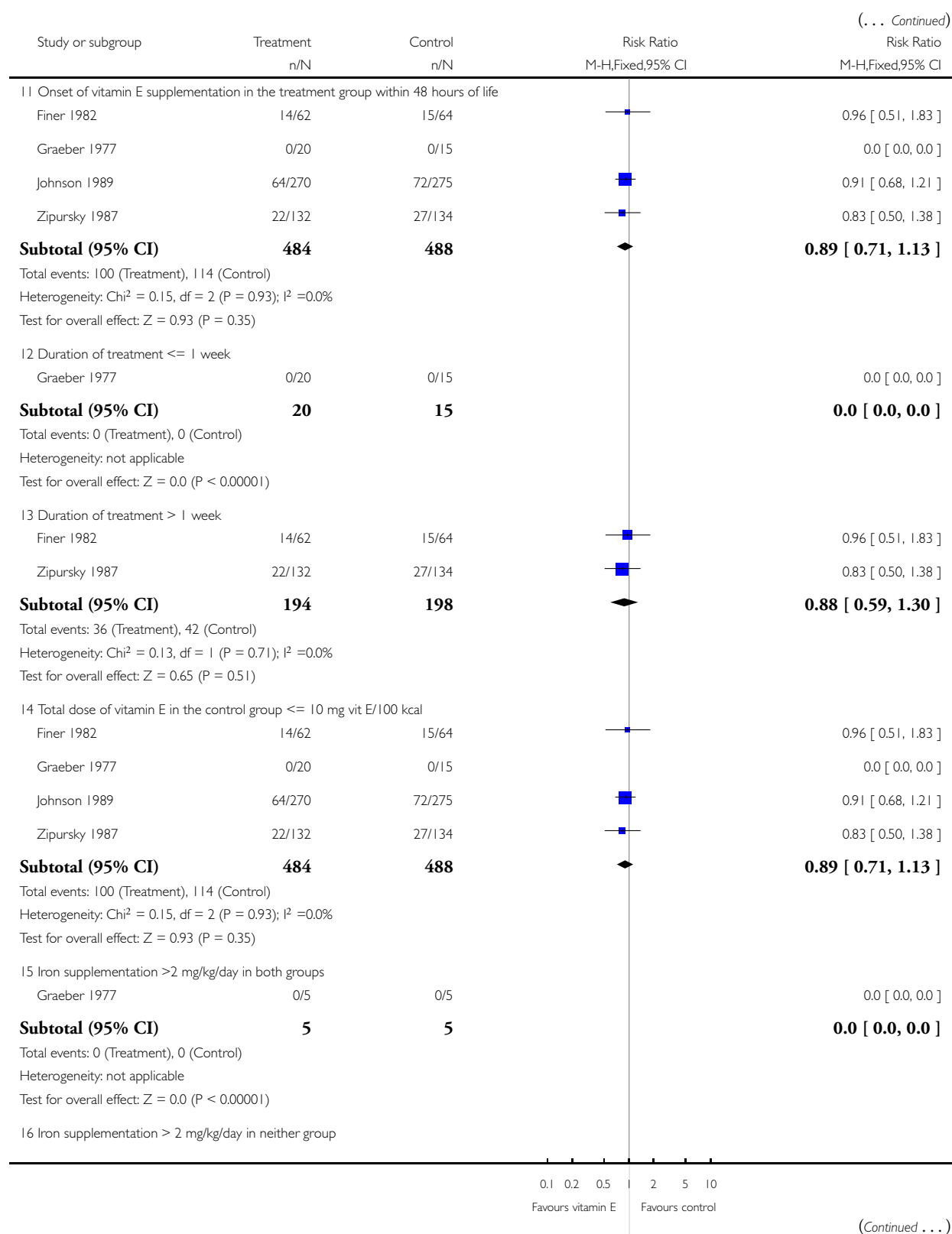
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

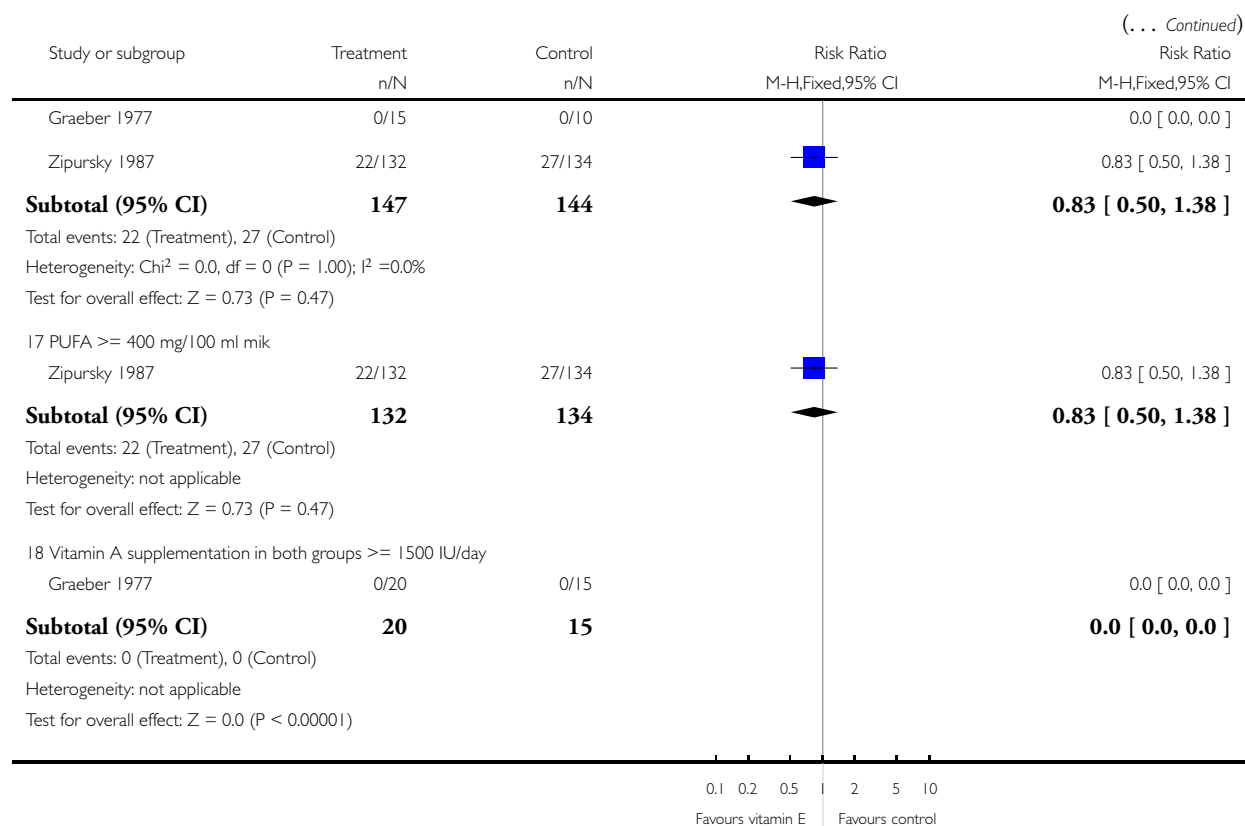
Outcome: 4 Bronchopulmonary dysplasia among very low birth weight infants









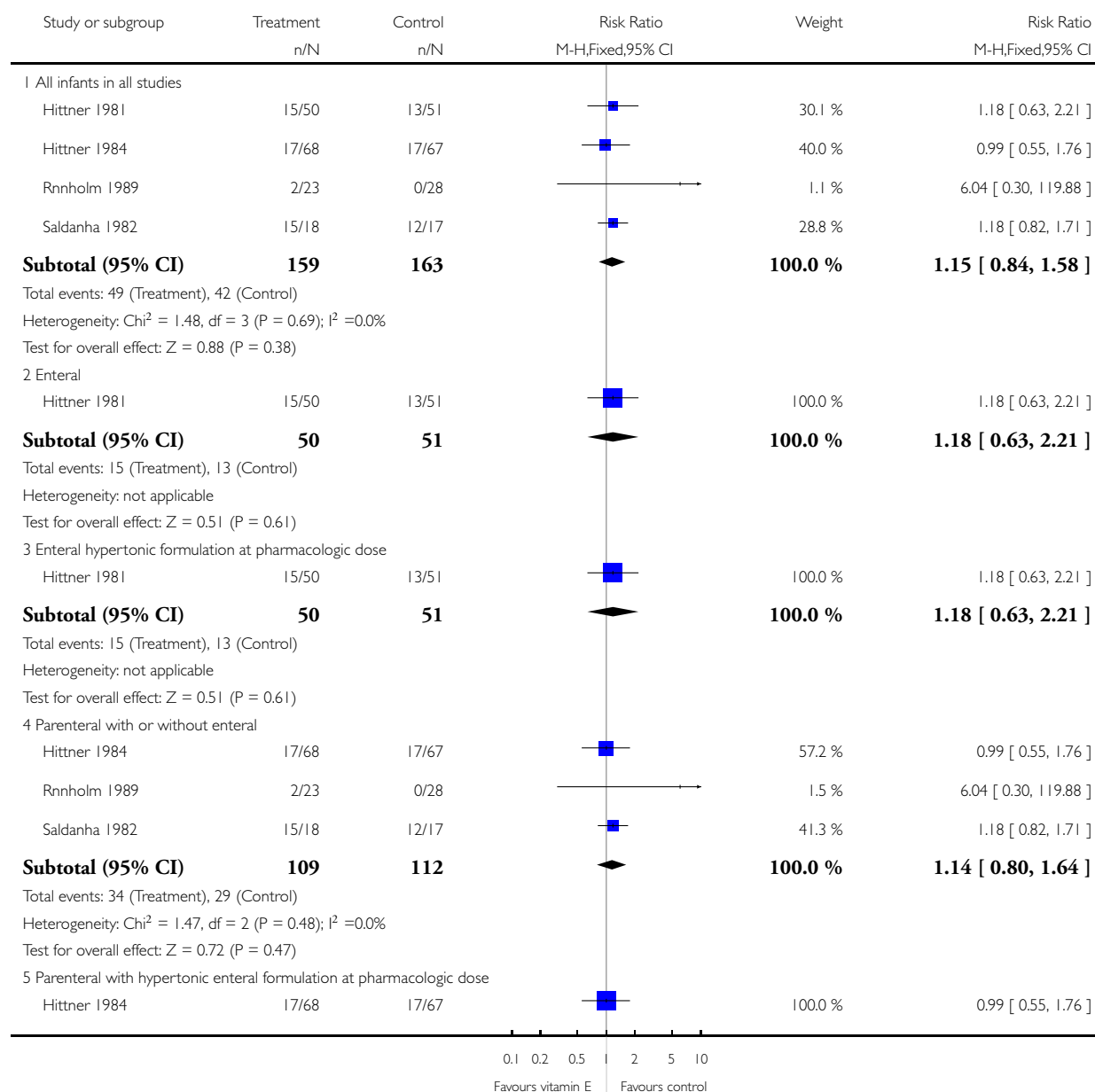


### Analysis 1.5. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 5 Bronchopulmonary dysplasia among surviving patients.

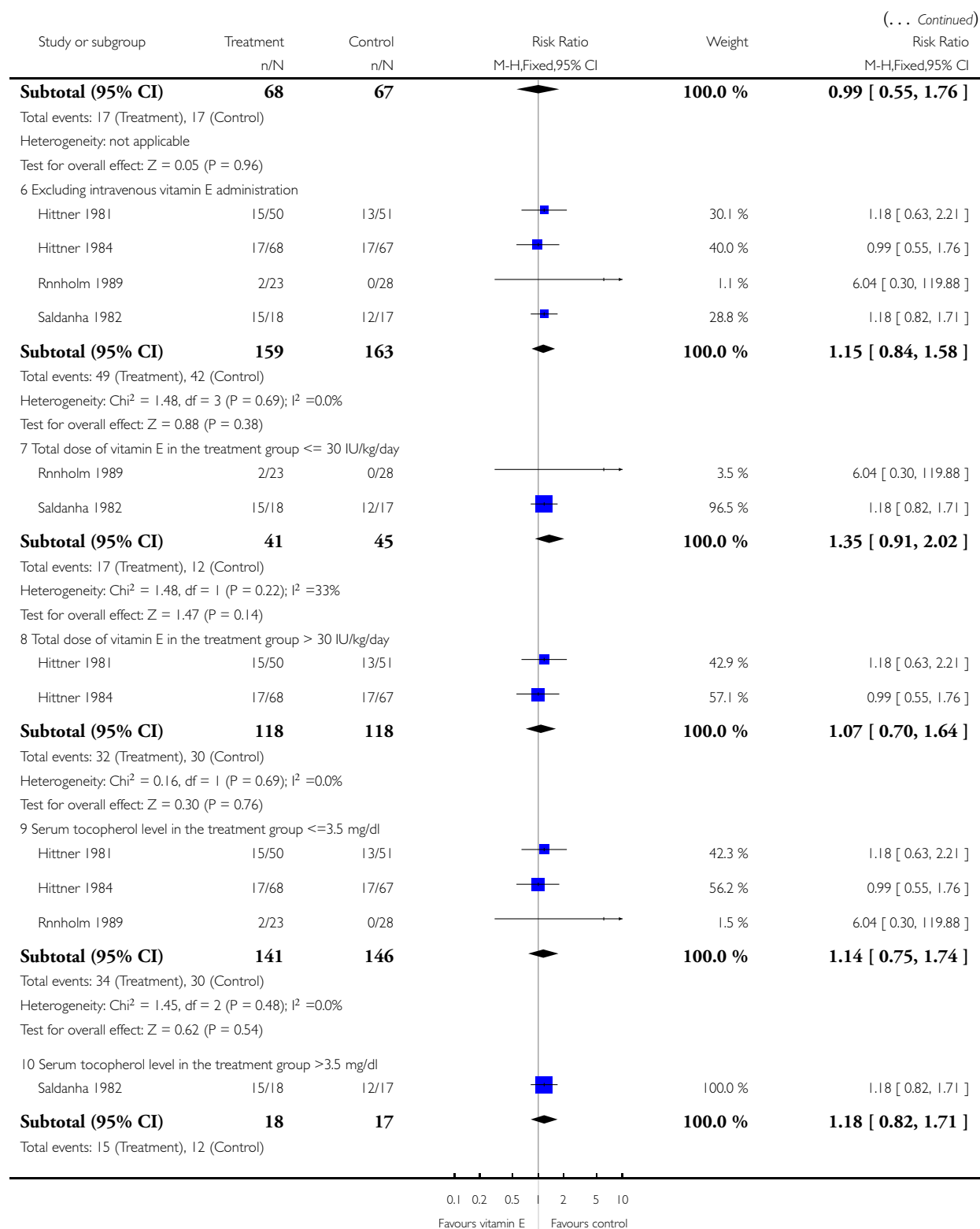
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

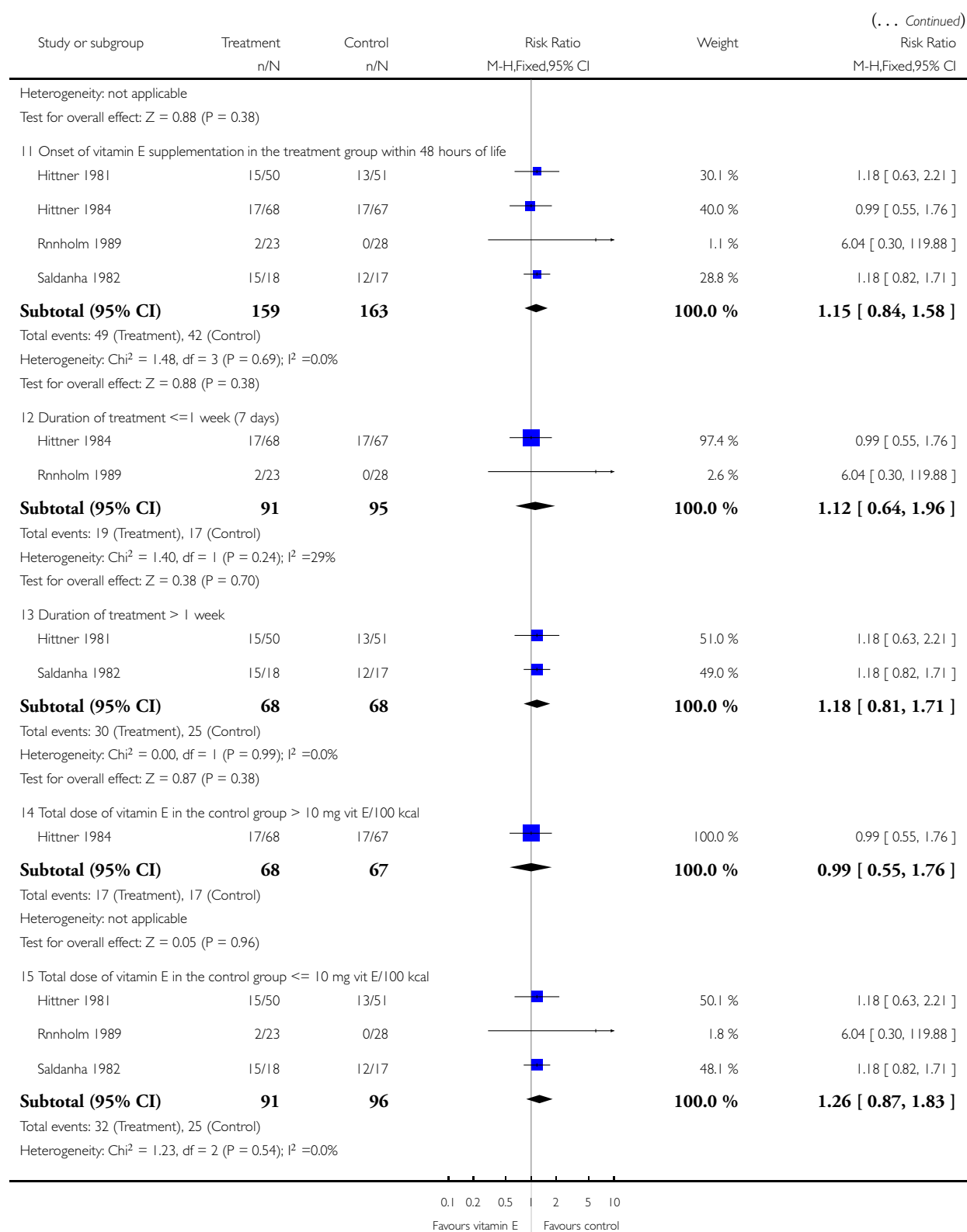
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 5 Bronchopulmonary dysplasia among surviving patients

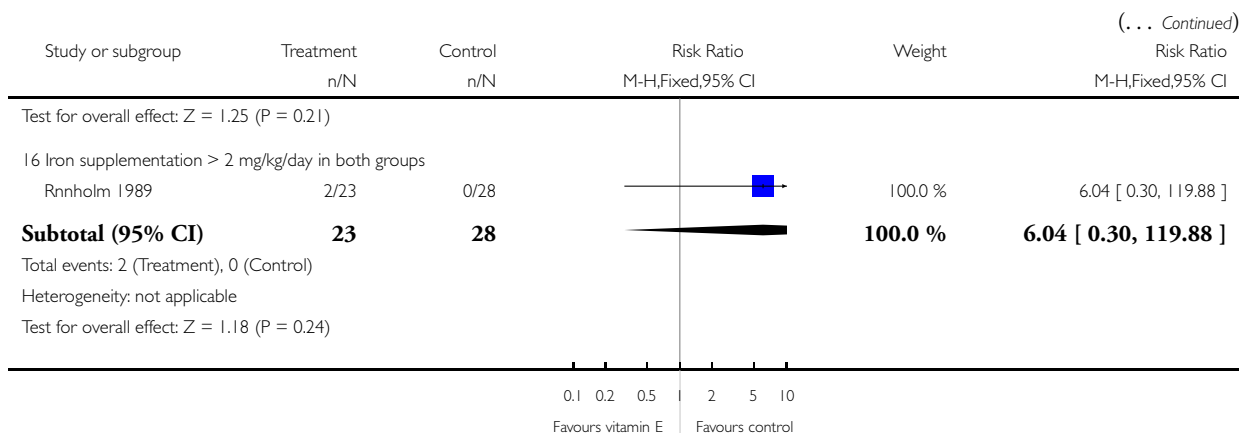


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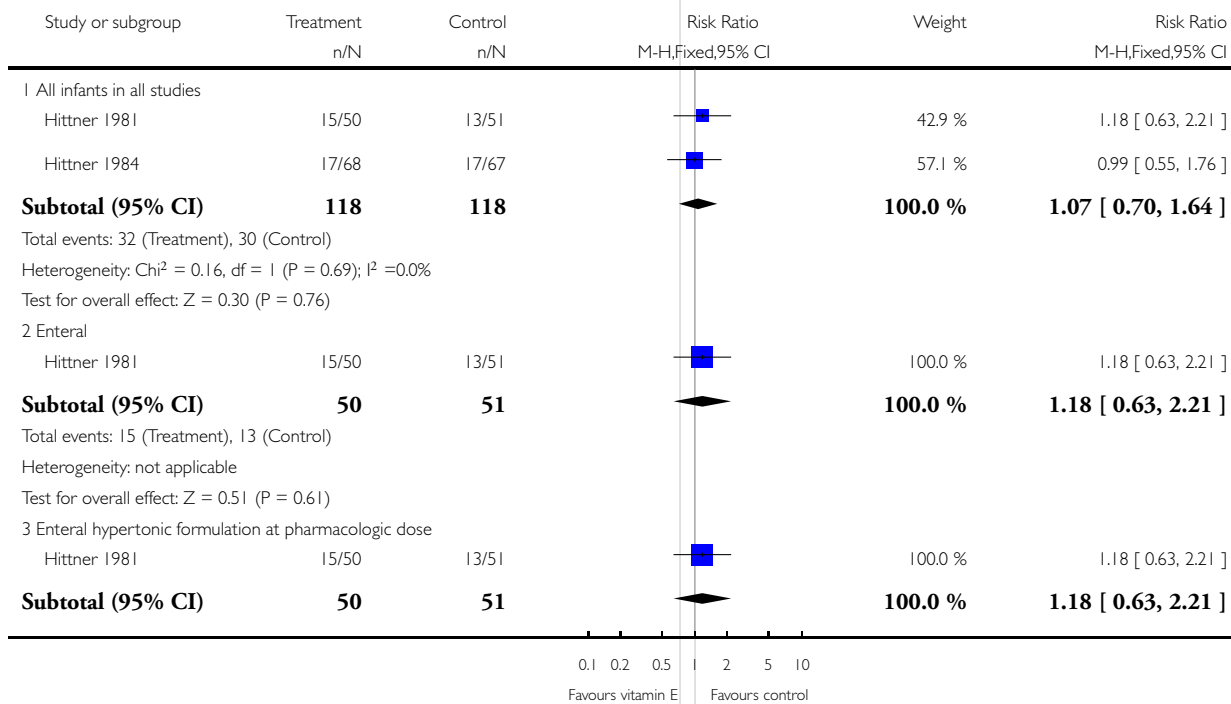


### Analysis 1.6. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 6 Bronchopulmonary dysplasia among surviving very low birth weight infants.

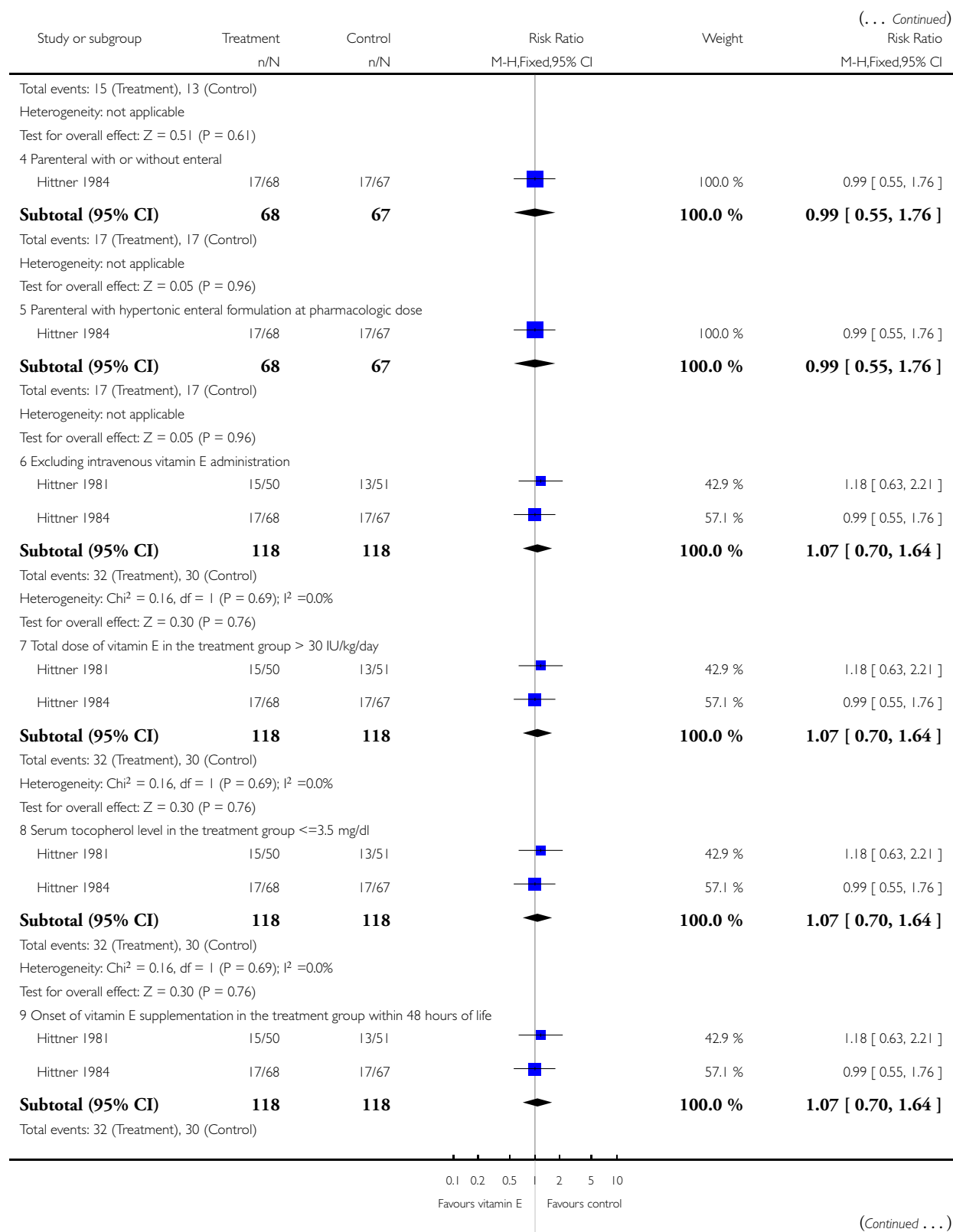
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

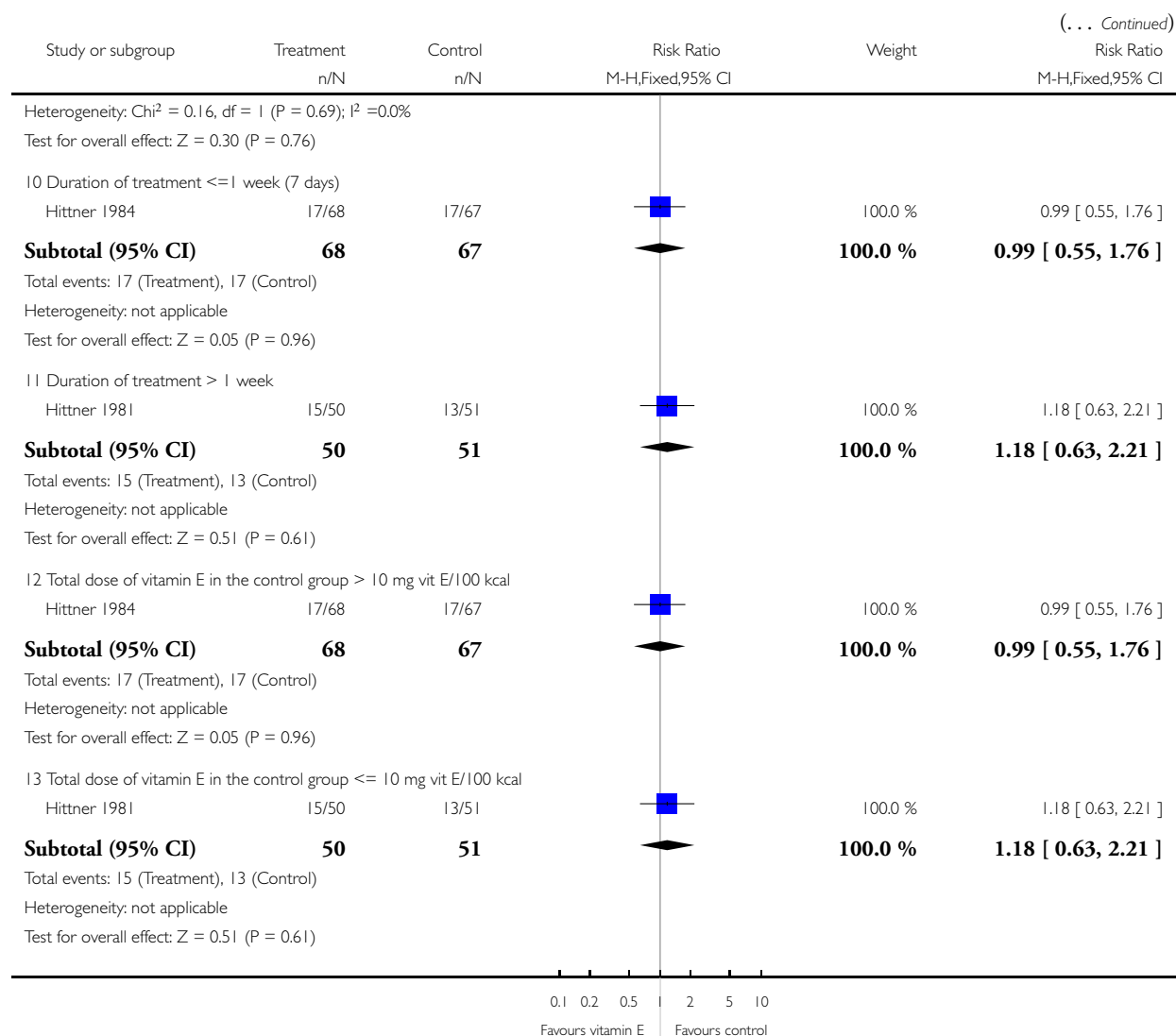
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 6 Bronchopulmonary dysplasia among surviving very low birth weight infants



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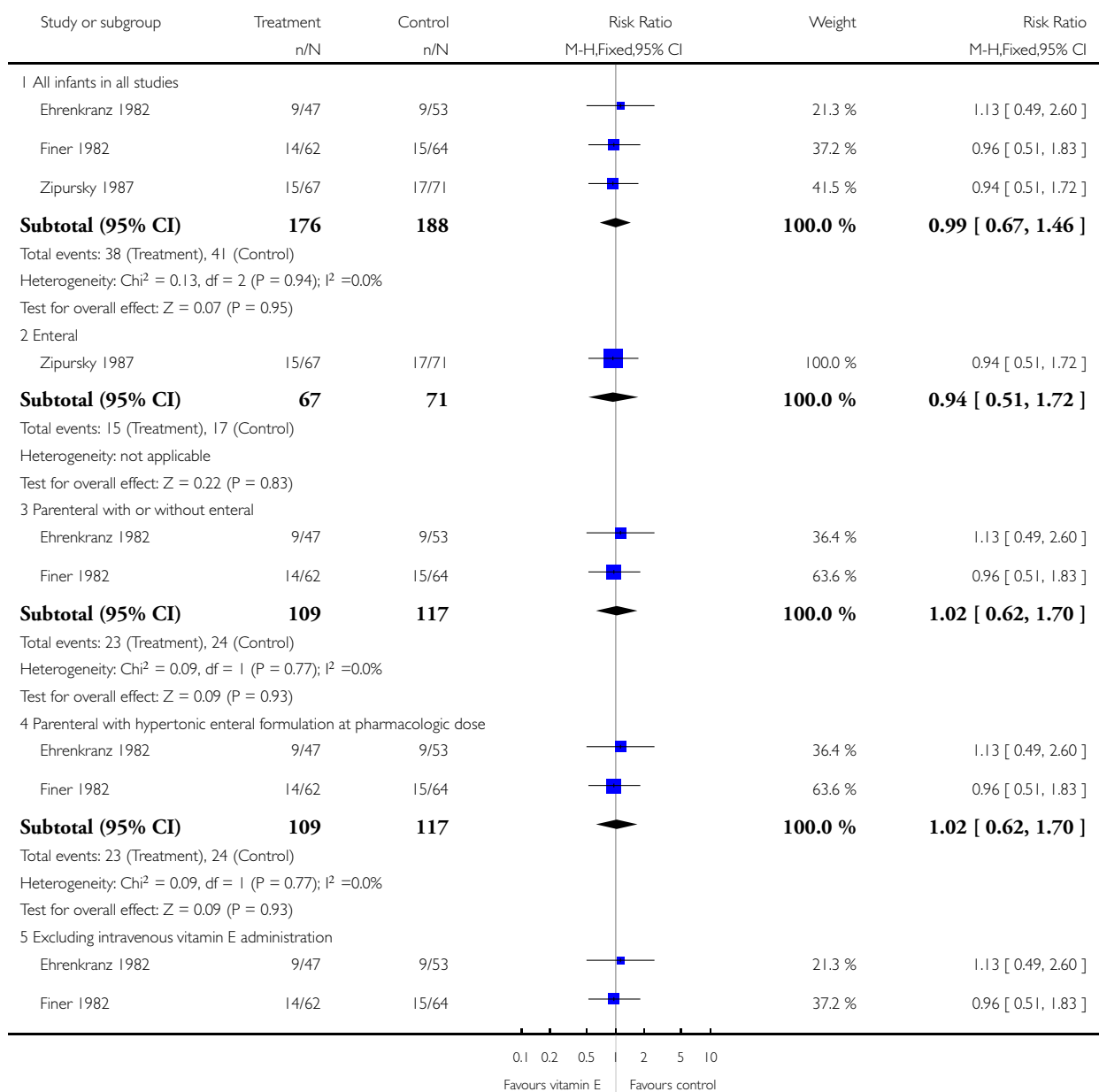


# **Analysis 1.7. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 7 Radiographic signs of bronchopulmonary dysplasia persistent at 6 weeks - 2 months.**

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

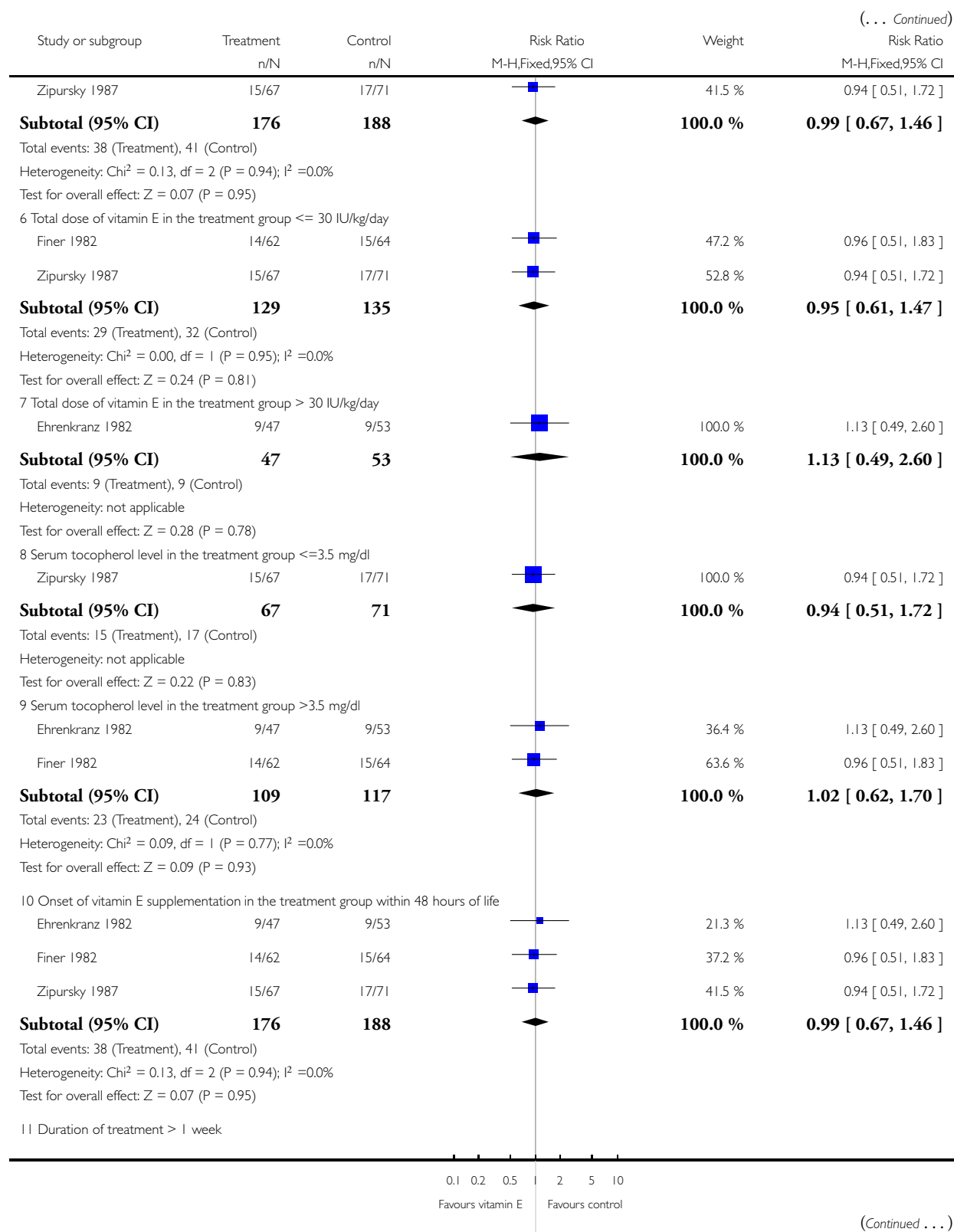
Comparison: 1 Vitamin E versus placebo or no vitamin E

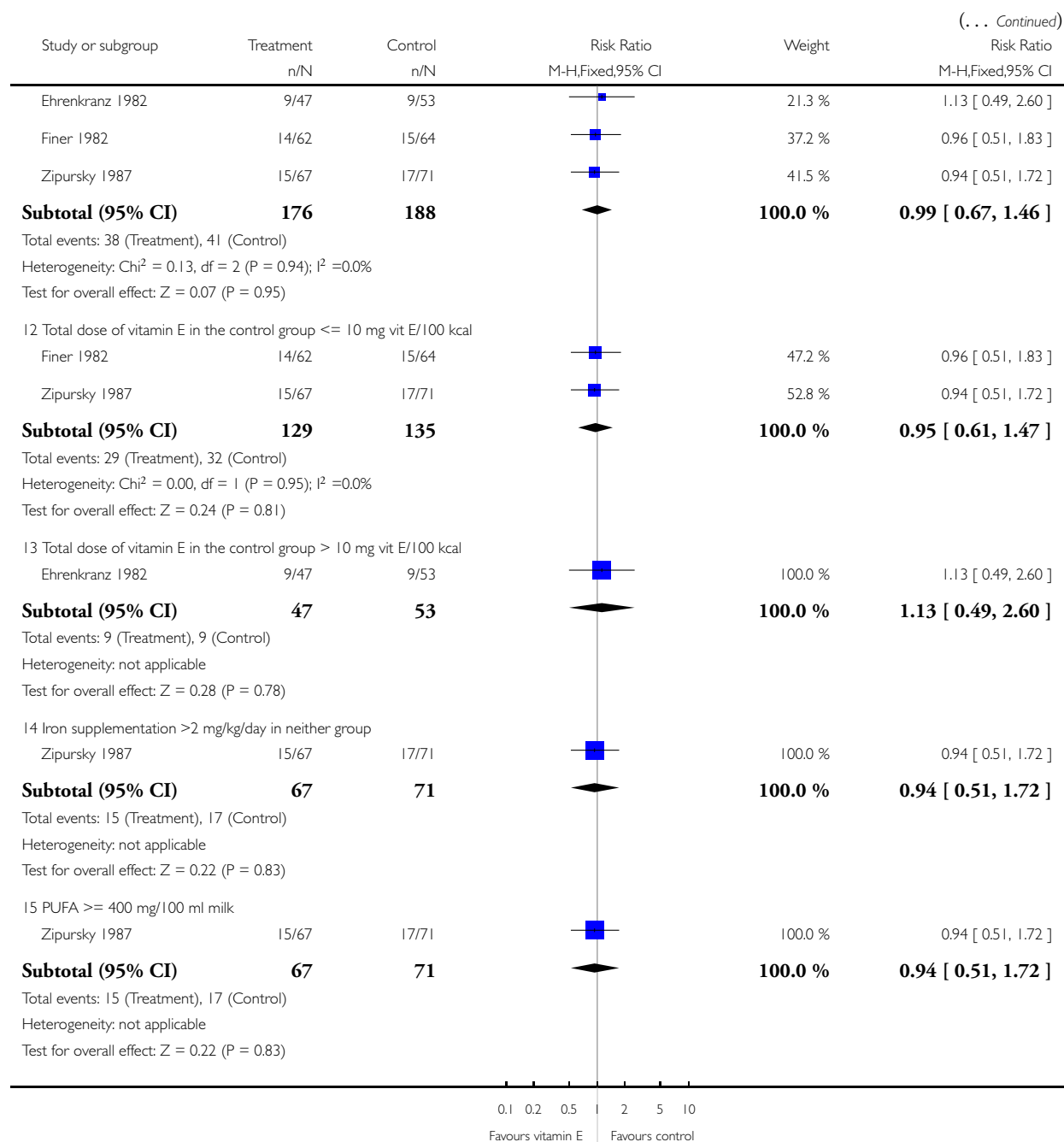
Outcome: 7 Radiographic signs of bronchopulmonary dysplasia persistent at 6 weeks - 2 months



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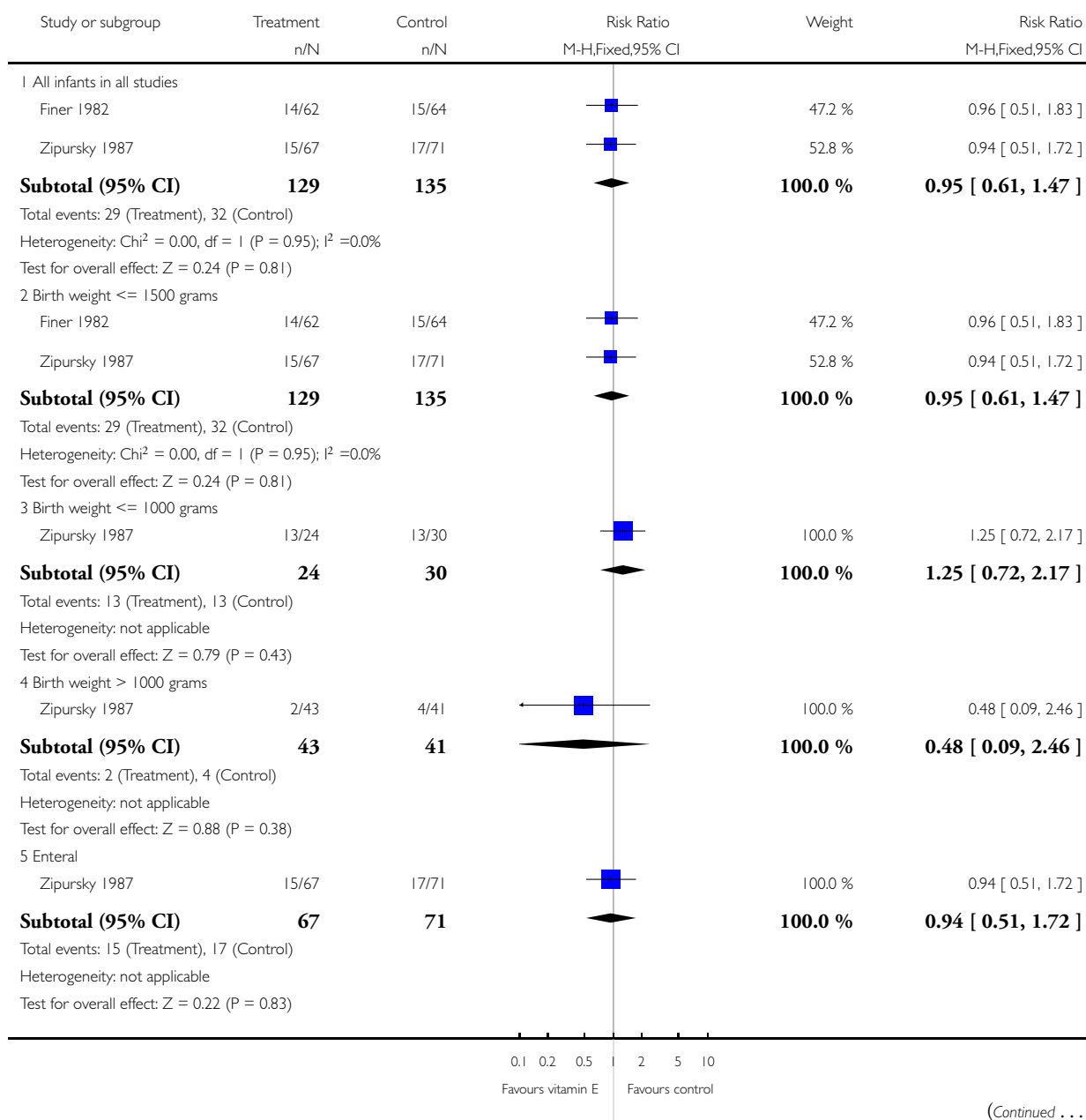


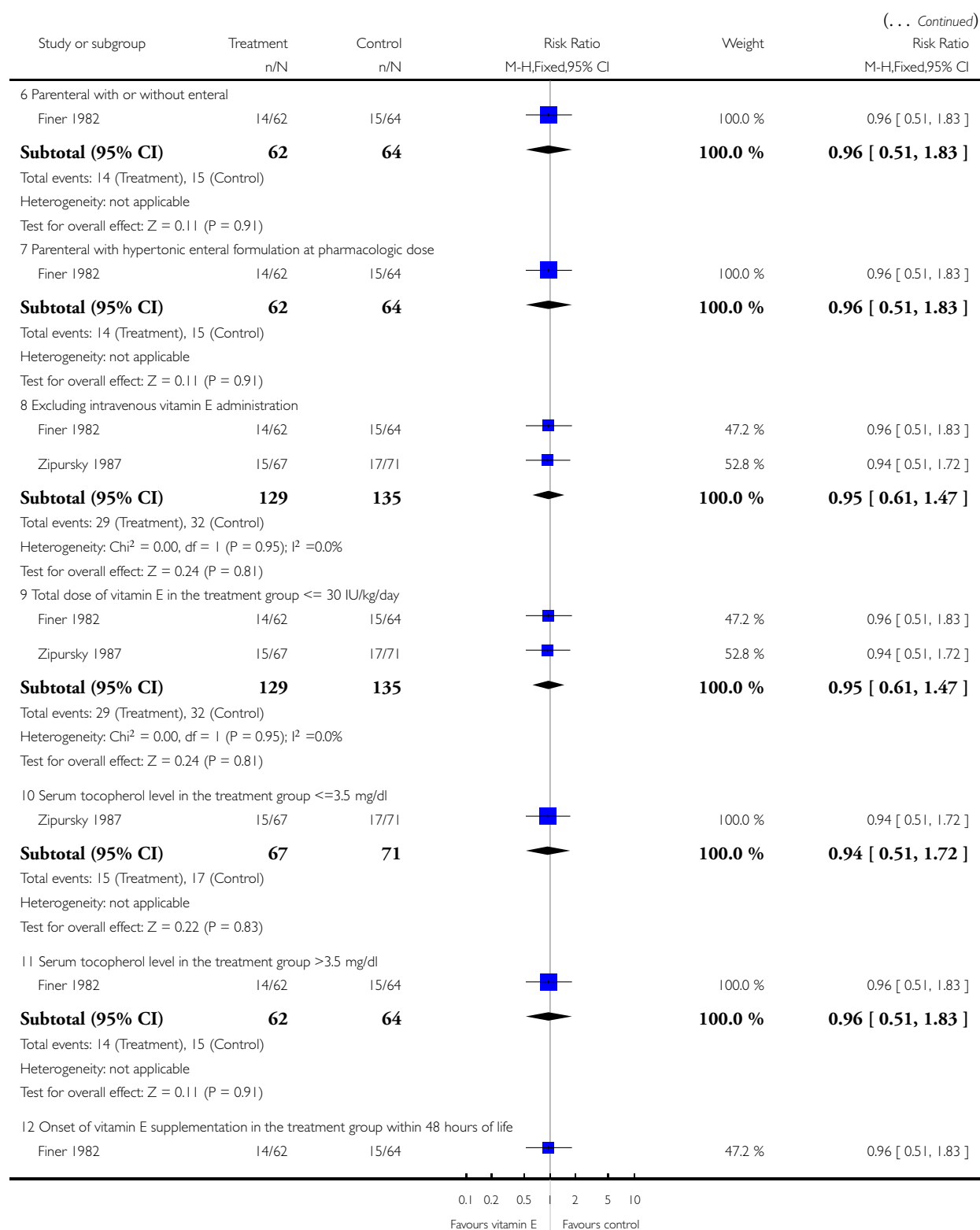
# **Analysis 1.8. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 8 Radiographic signs of bronchopulmonary dysplasia at 6 weeks - 2 months among very low birth weight infants.**

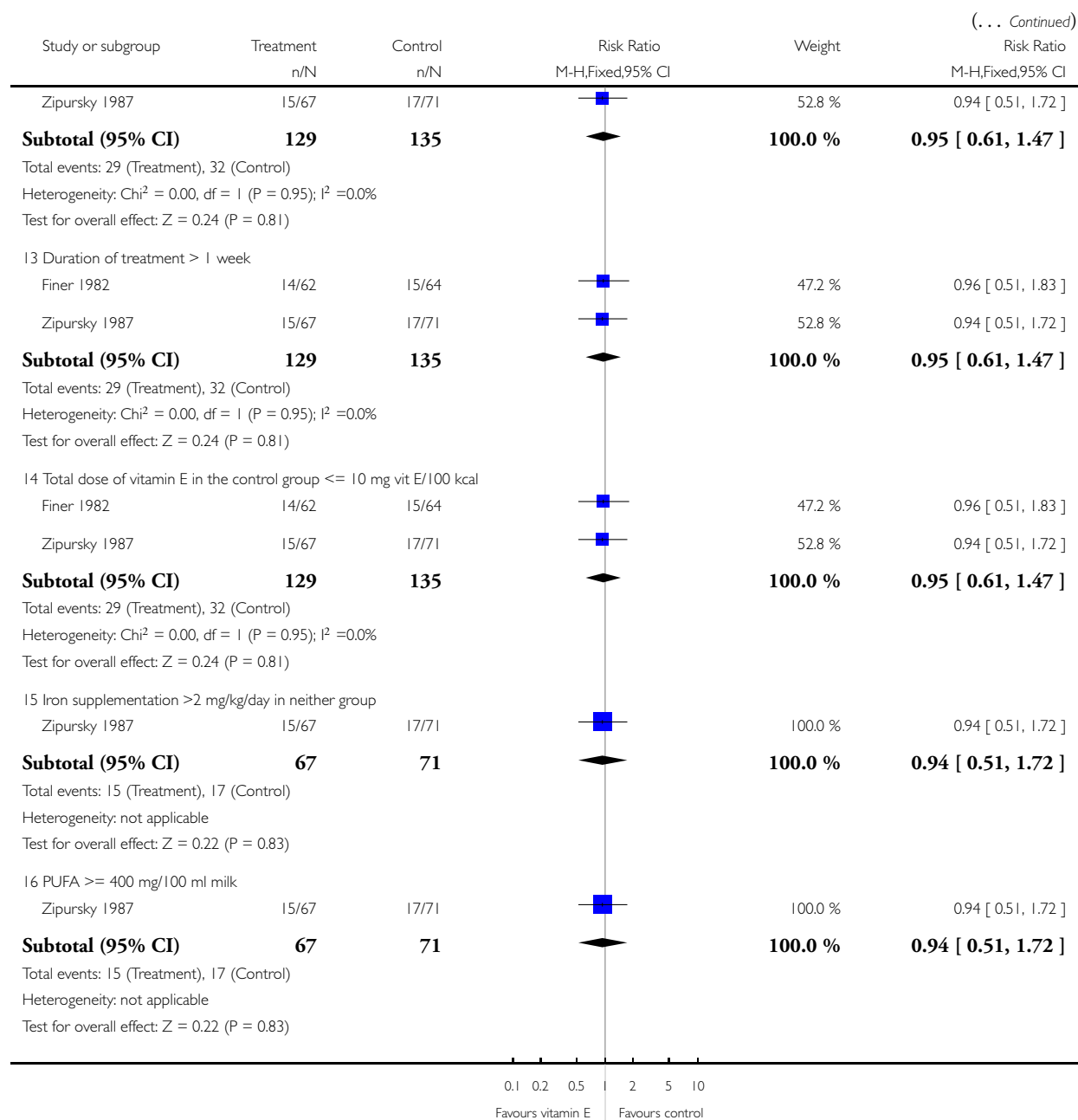
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 8 Radiographic signs of bronchopulmonary dysplasia at 6 weeks - 2 months among very low birth weight infants





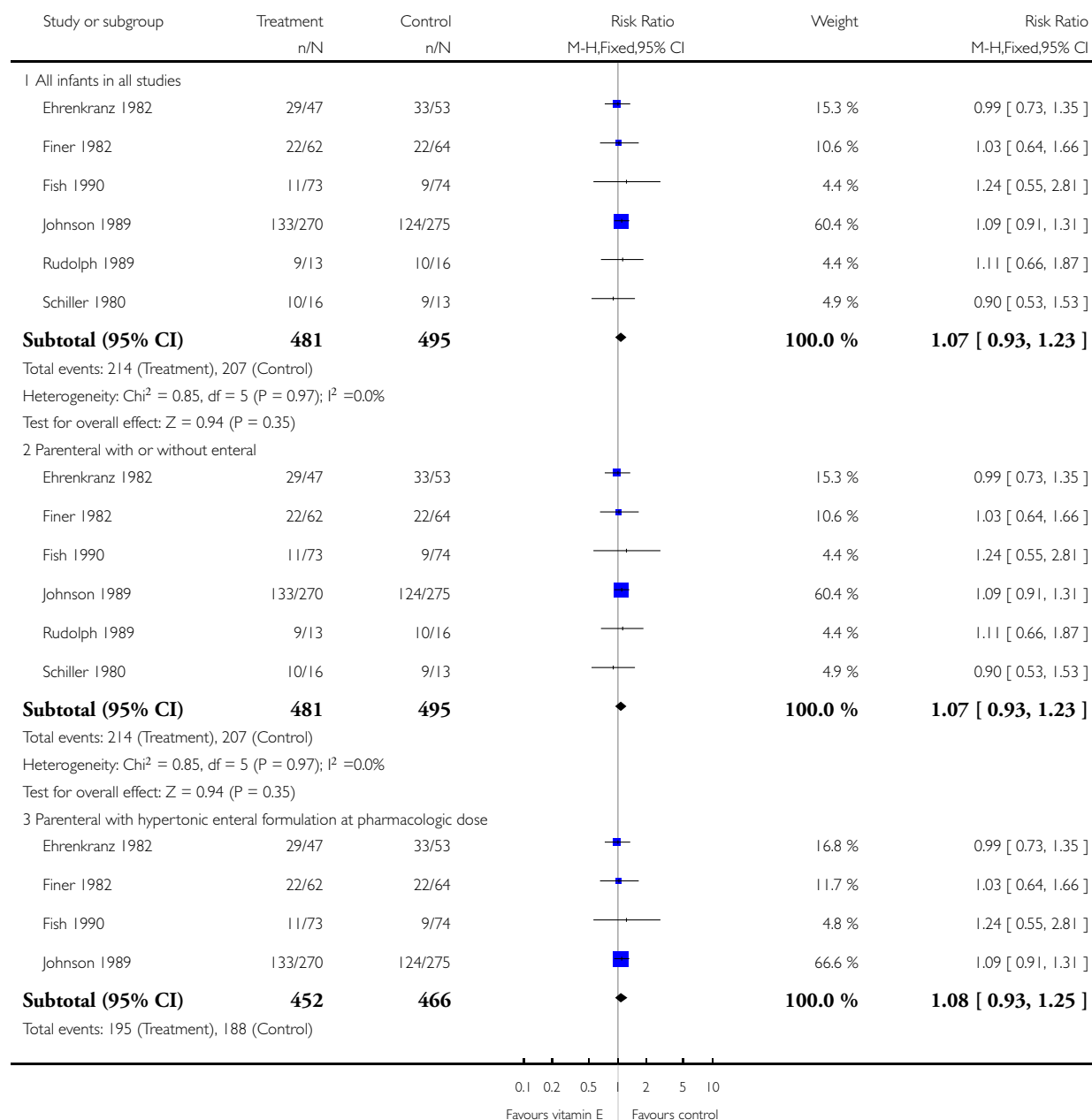


## Analysis 1.9. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 9 Patent ductus arteriosus.

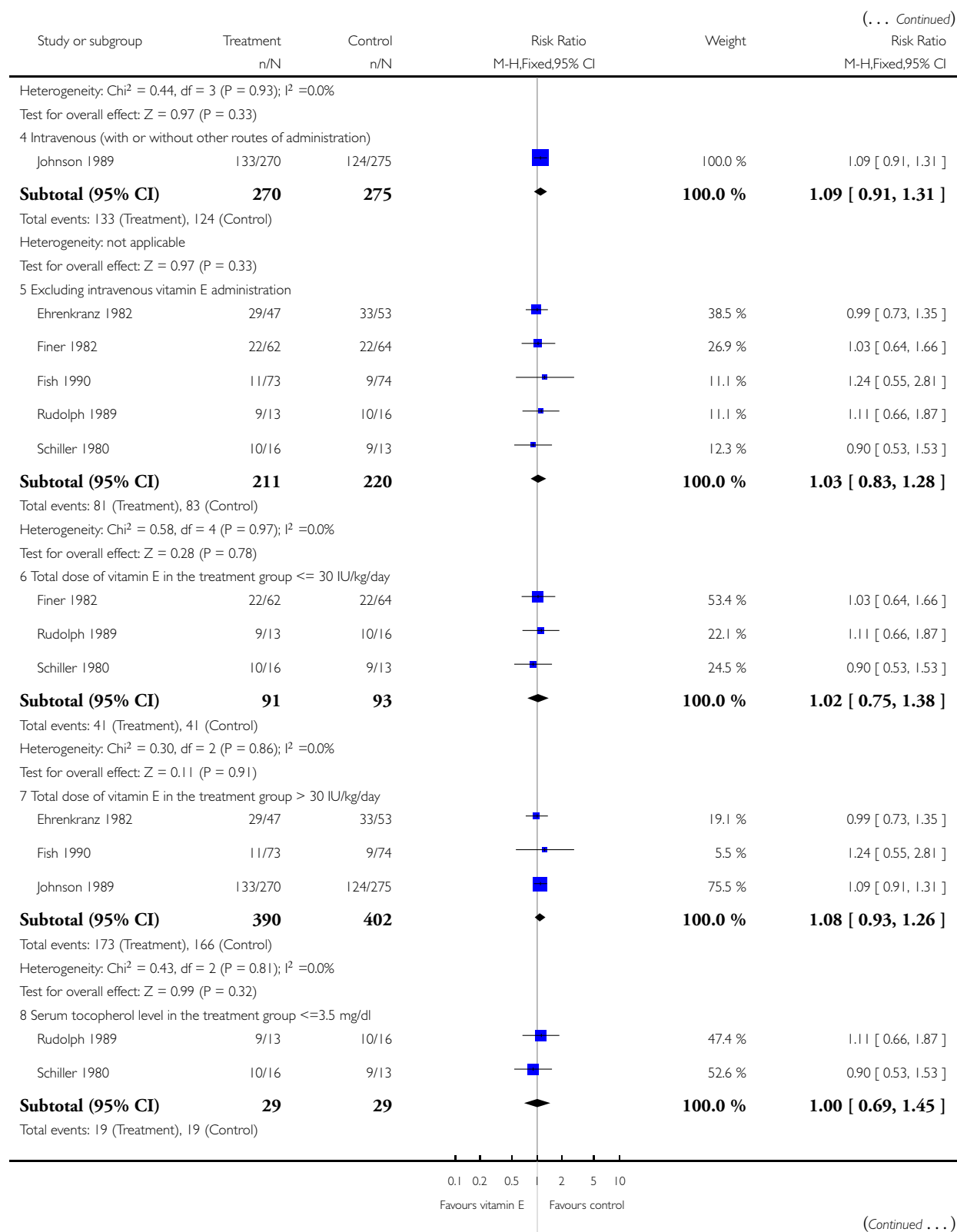
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

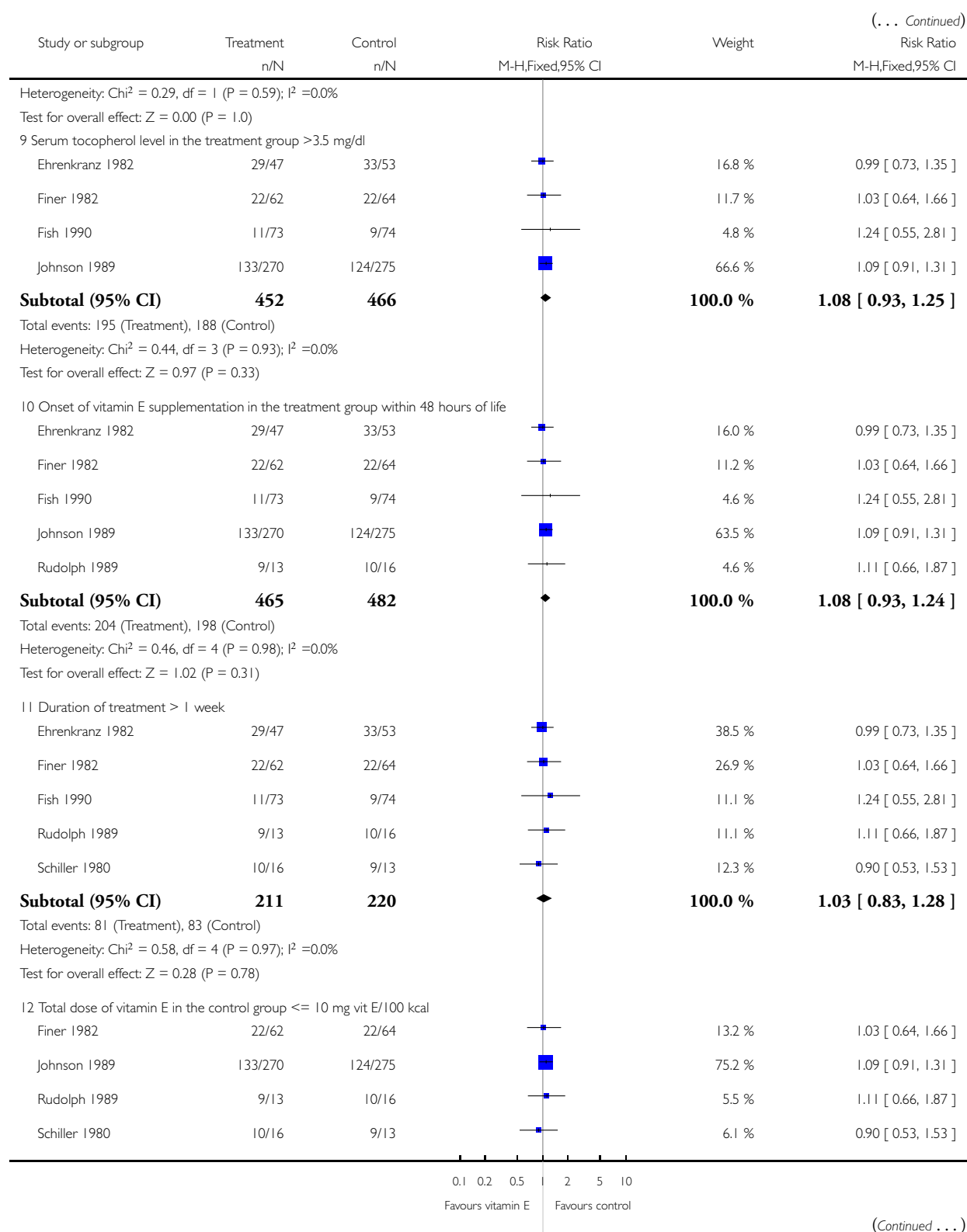
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 9 Patent ductus arteriosus

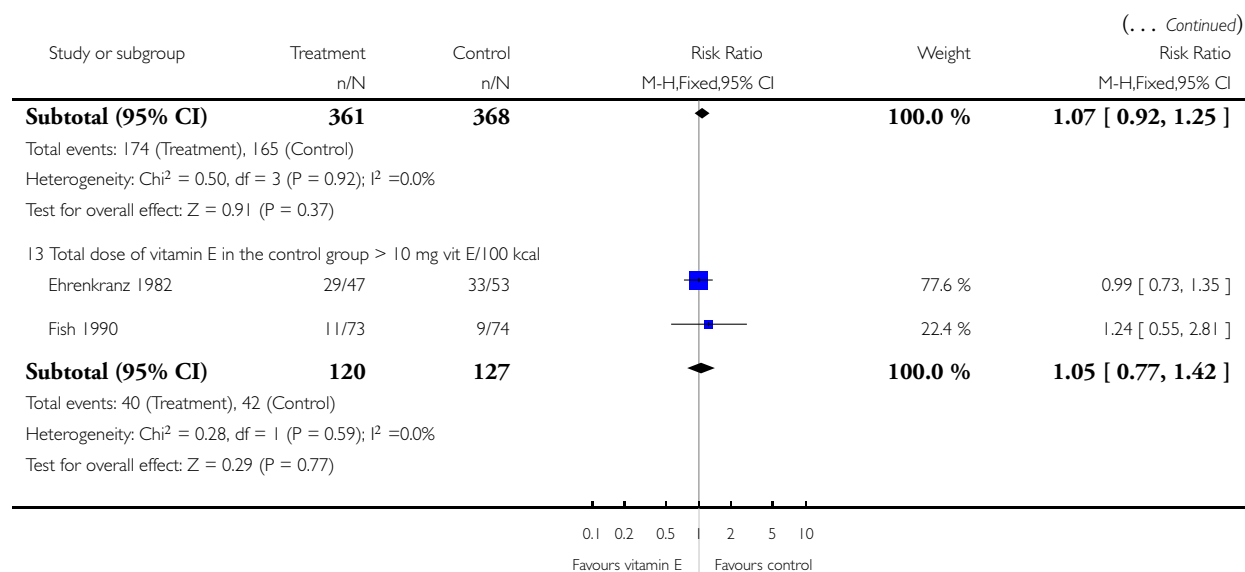


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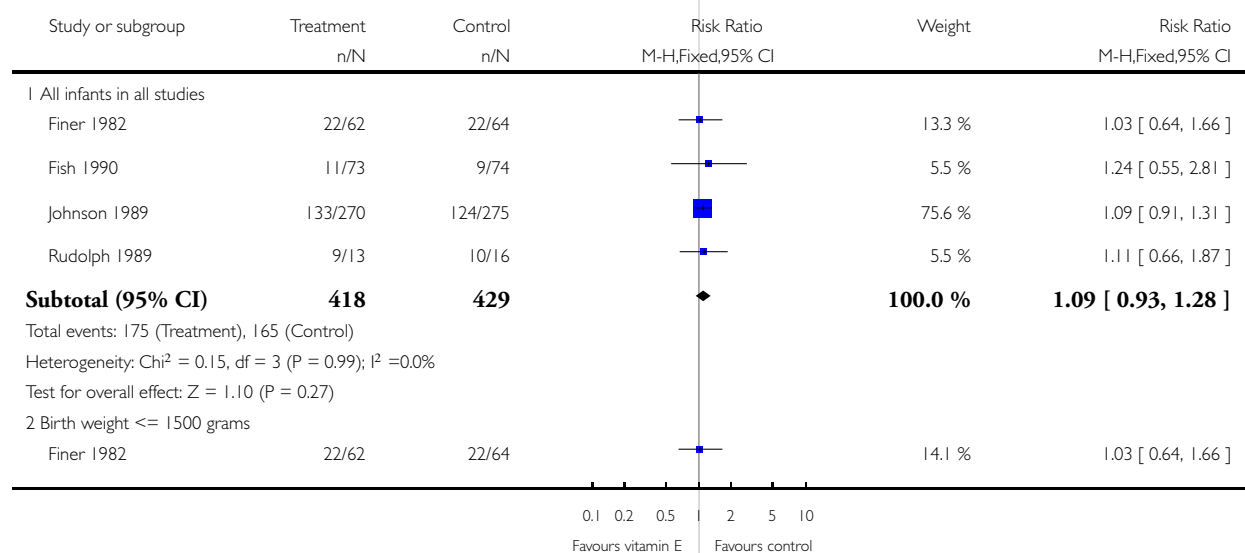


### Analysis 1.10. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 10 Patent ductus arteriosus among very low birth weight infants.

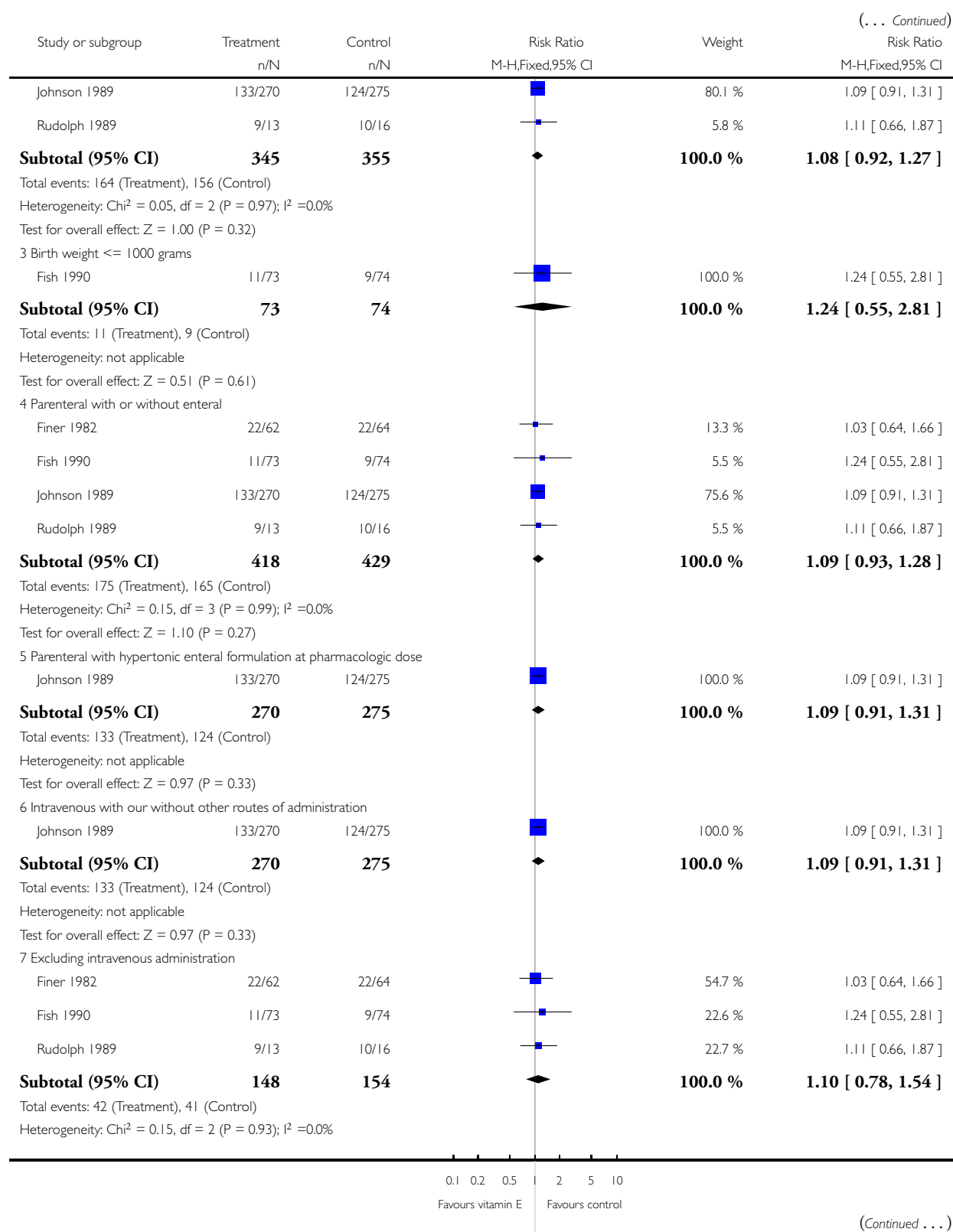
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

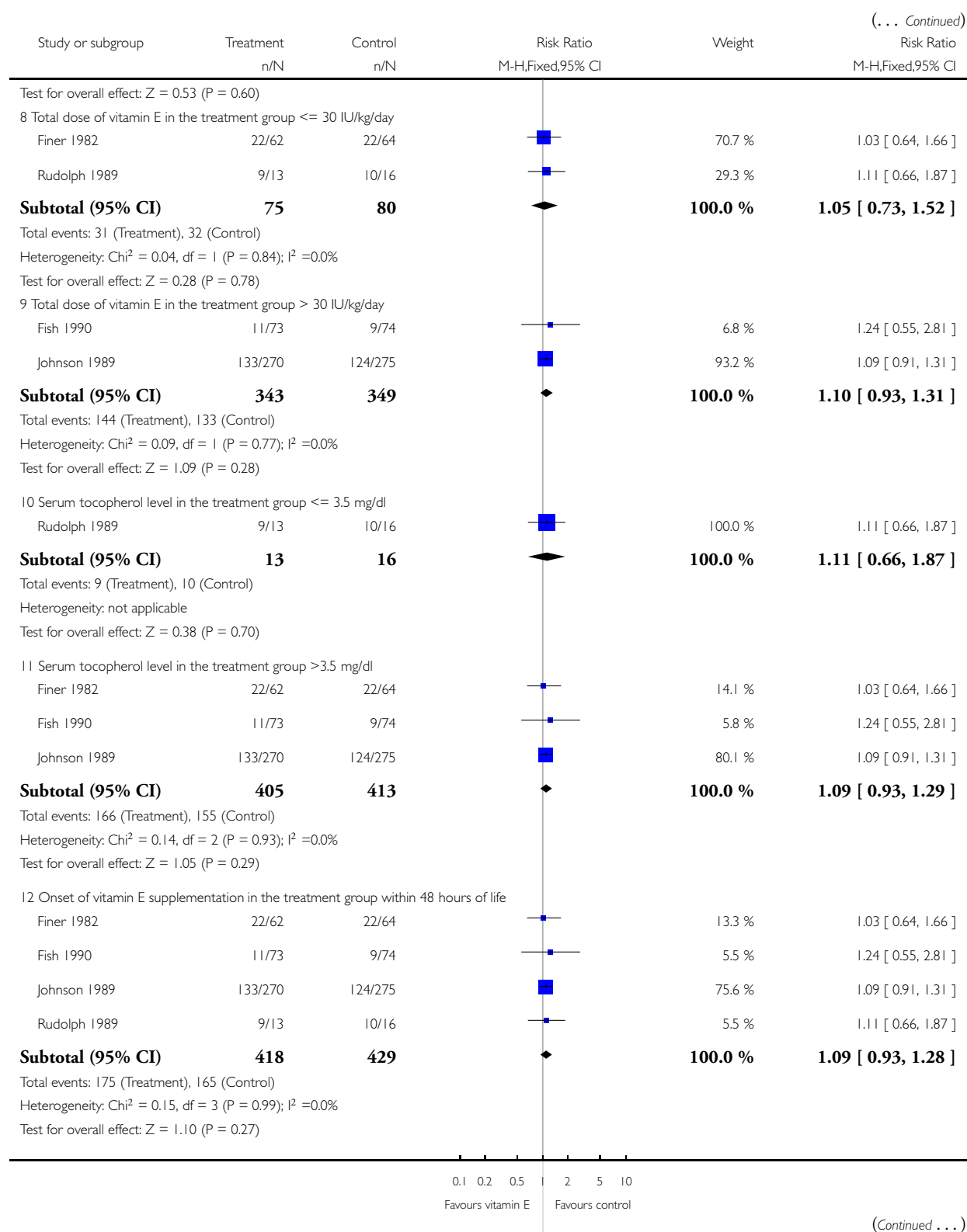
Comparison: 1 Vitamin E versus placebo or no vitamin E

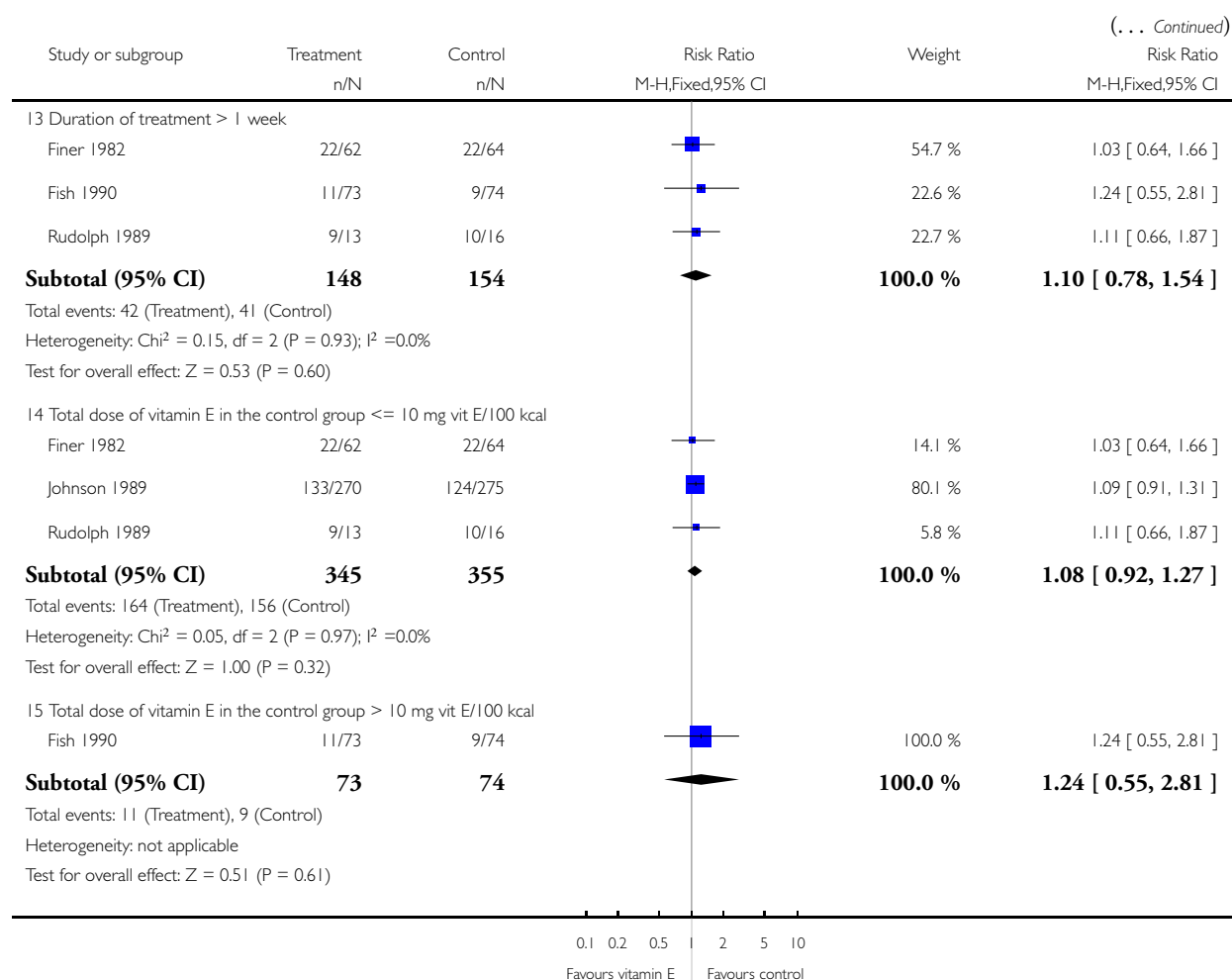
Outcome: 10 Patent ductus arteriosus among very low birth weight infants



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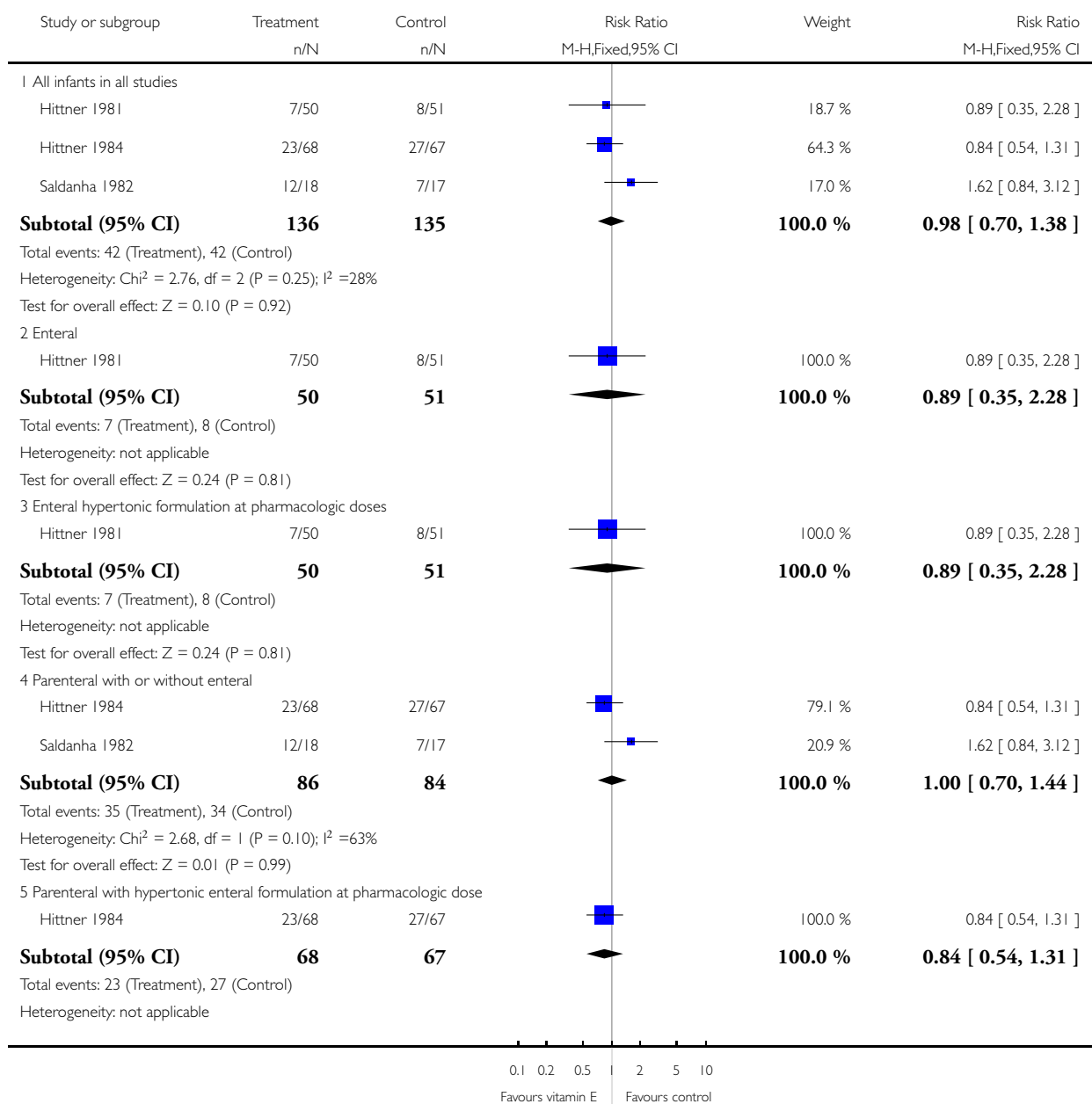


### Analysis 1.11. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 11 Patent ductus arteriosus among surviving patients (at 10 days-10 weeks).

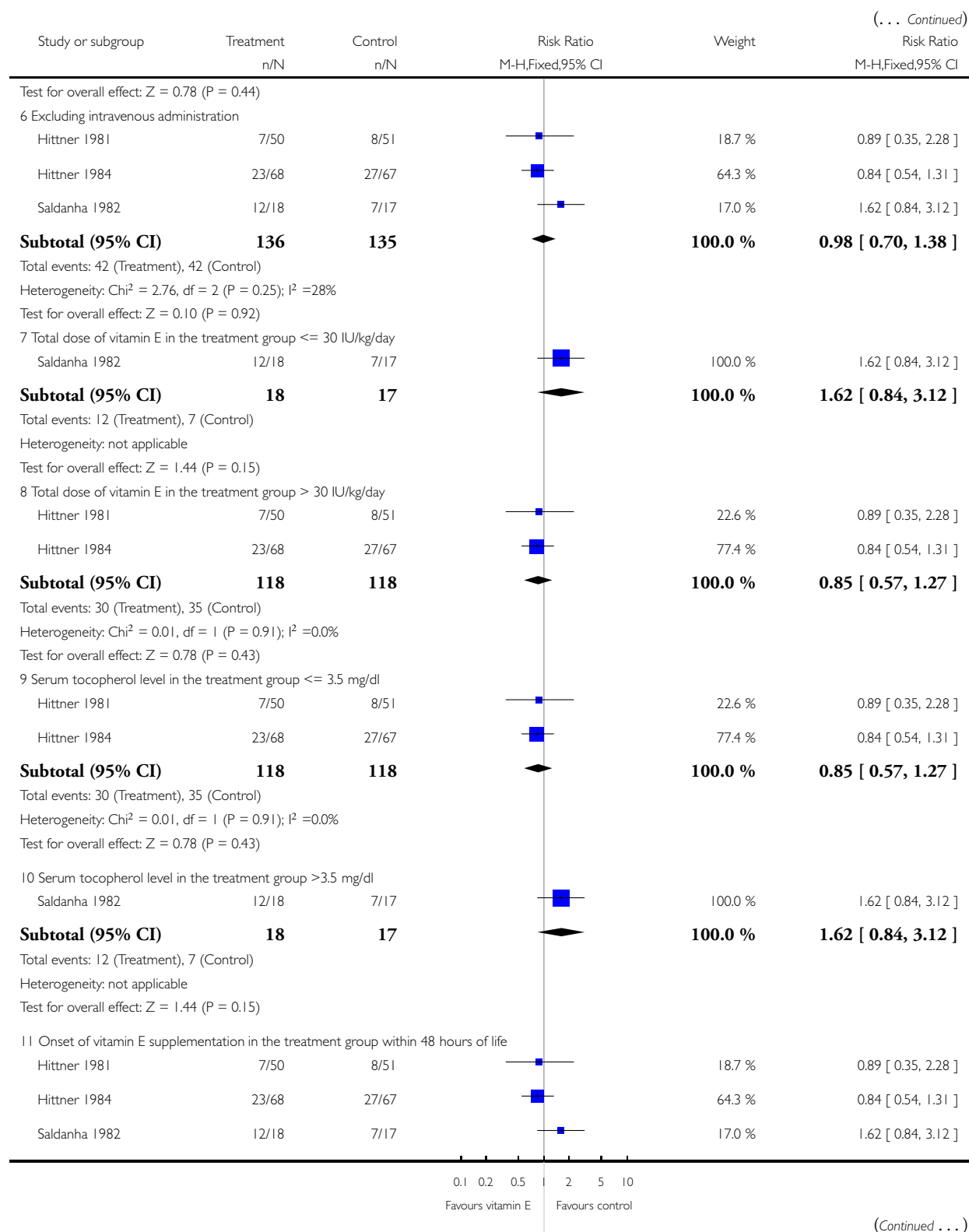
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

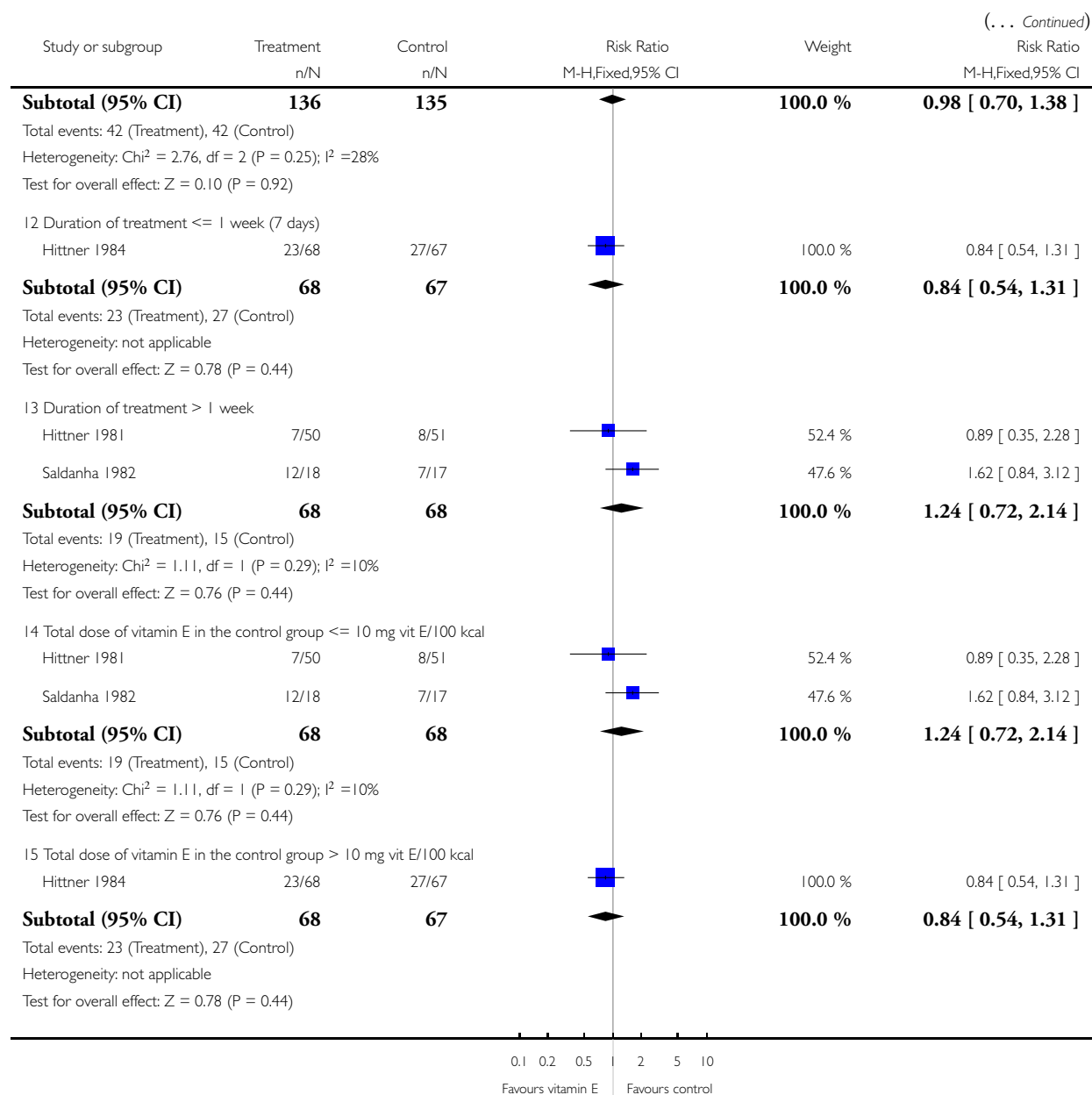
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 11 Patent ductus arteriosus among surviving patients (at 10 days-10 weeks)



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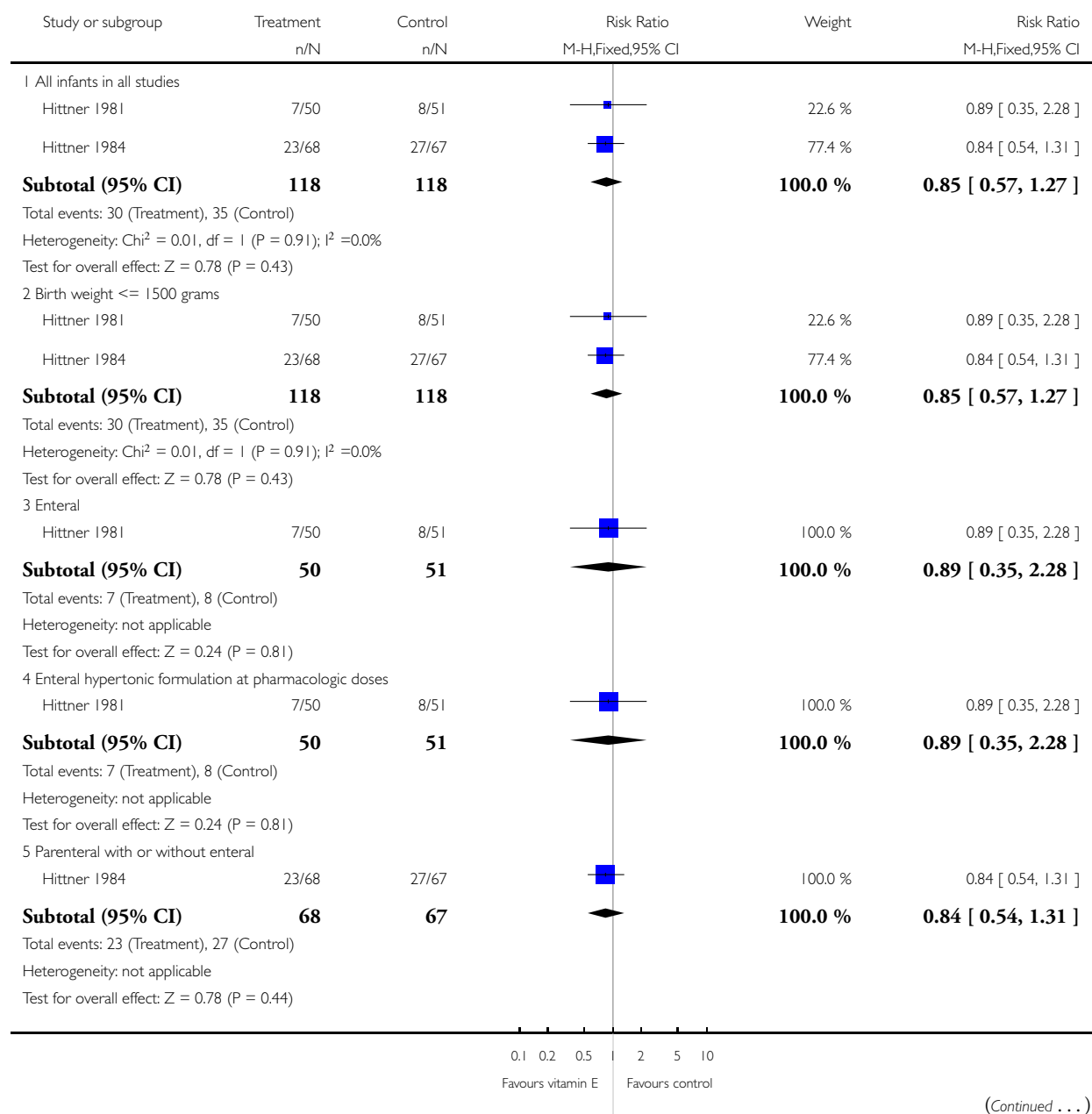


## Analysis 1.12. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 12 Patent ductus arteriosus among surviving very low birth infants (at 10 days-10 weeks).

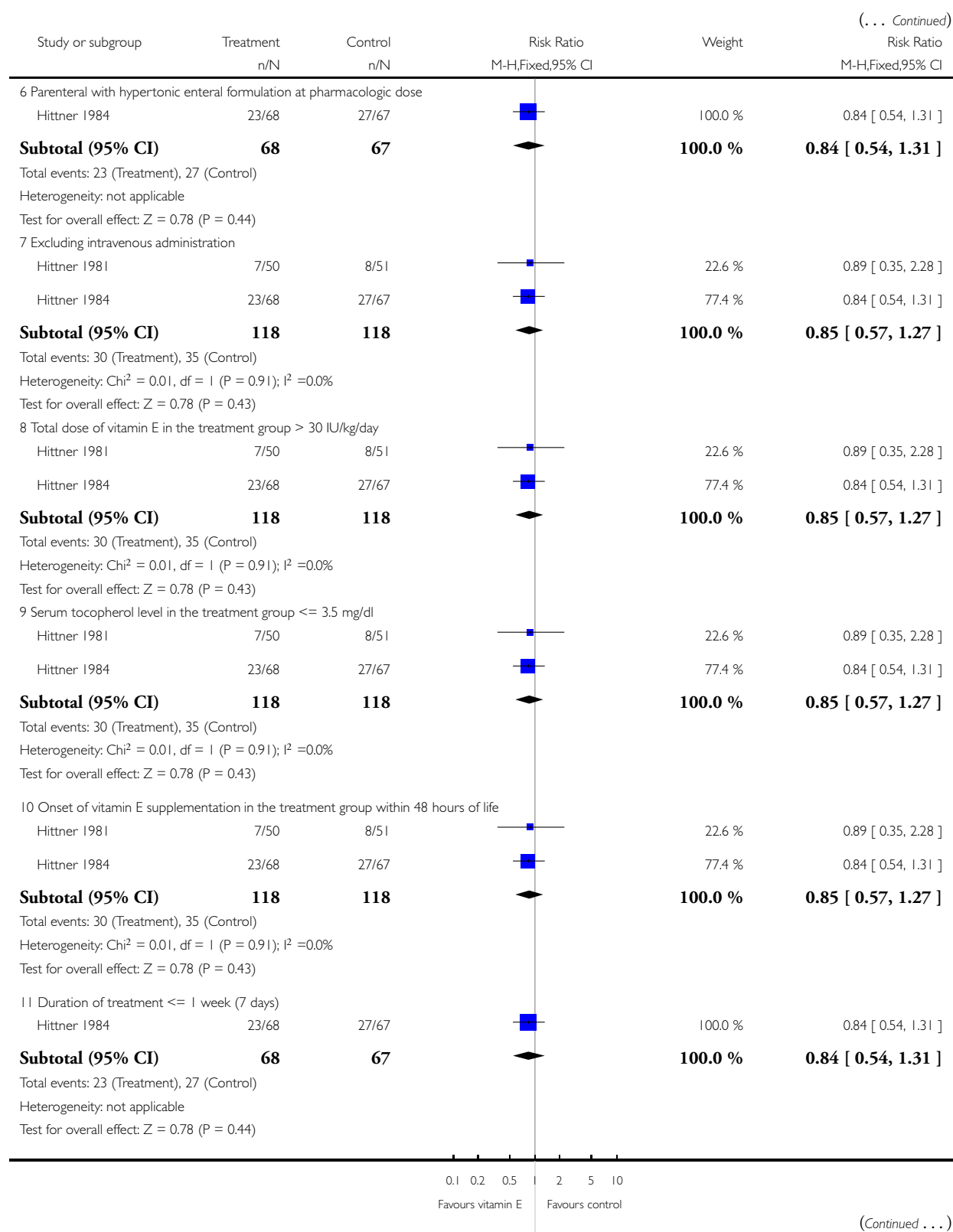
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

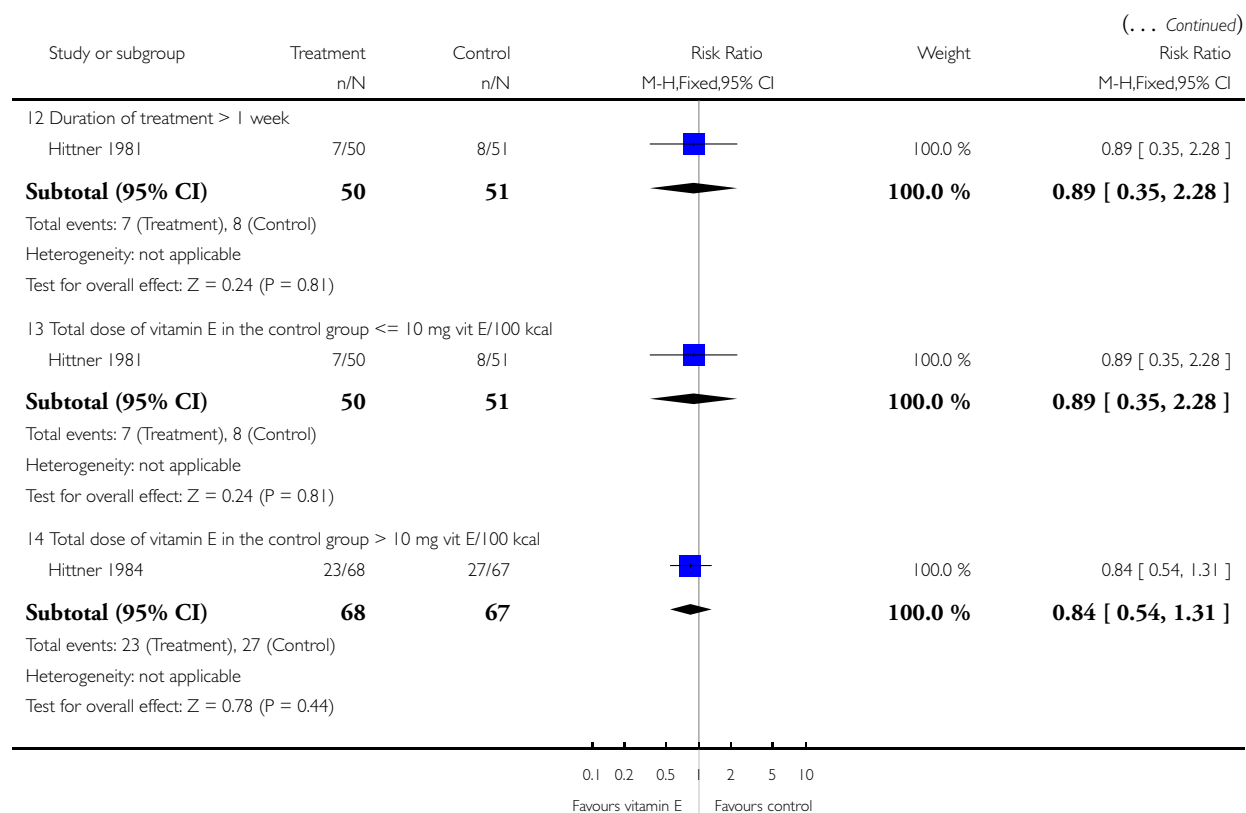
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 12 Patent ductus arteriosus among surviving very low birth infants (at 10 days-10 weeks)







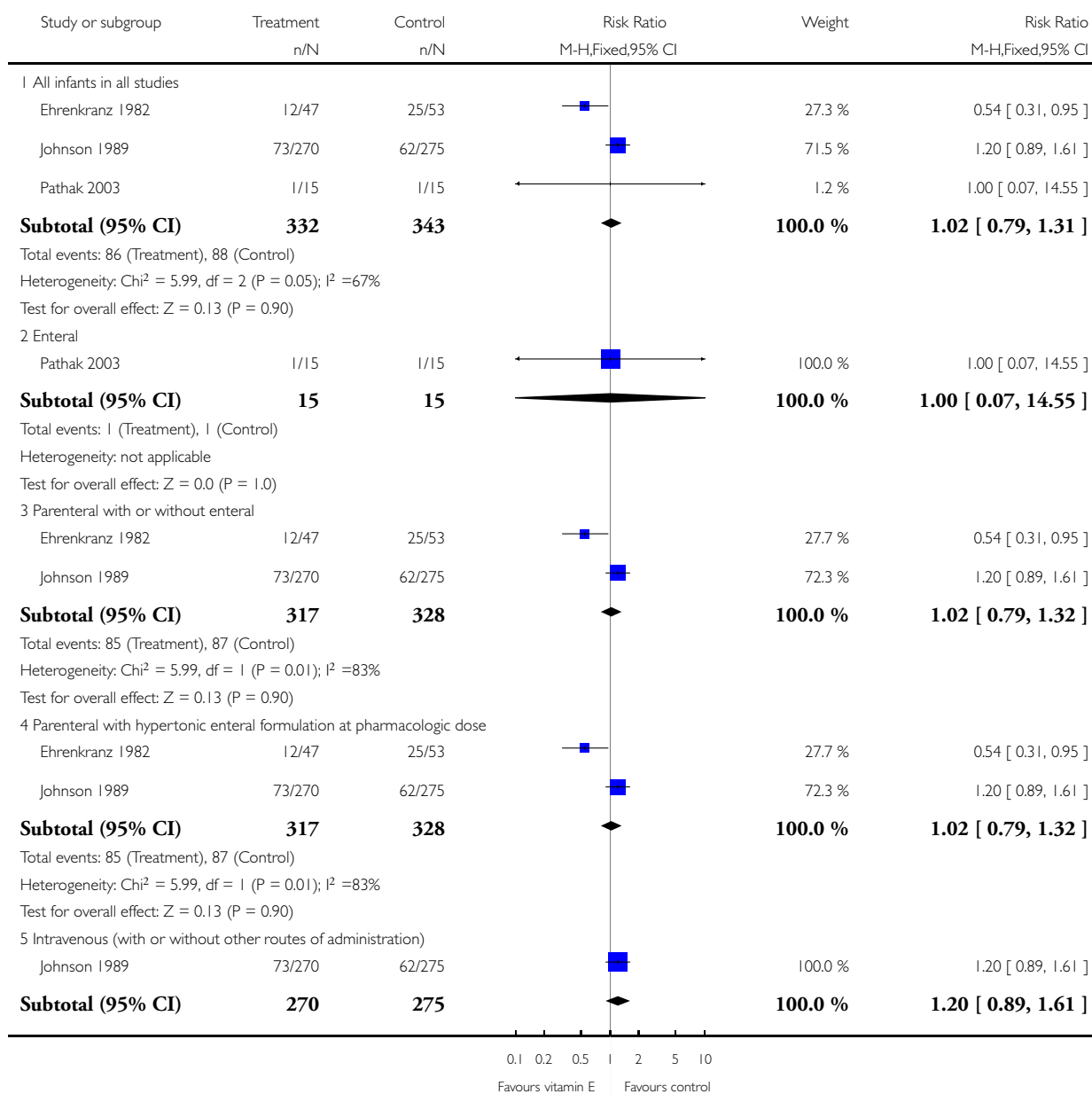


### Analysis 1.13. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 13 Patent ductus arteriosus requiring treatment.

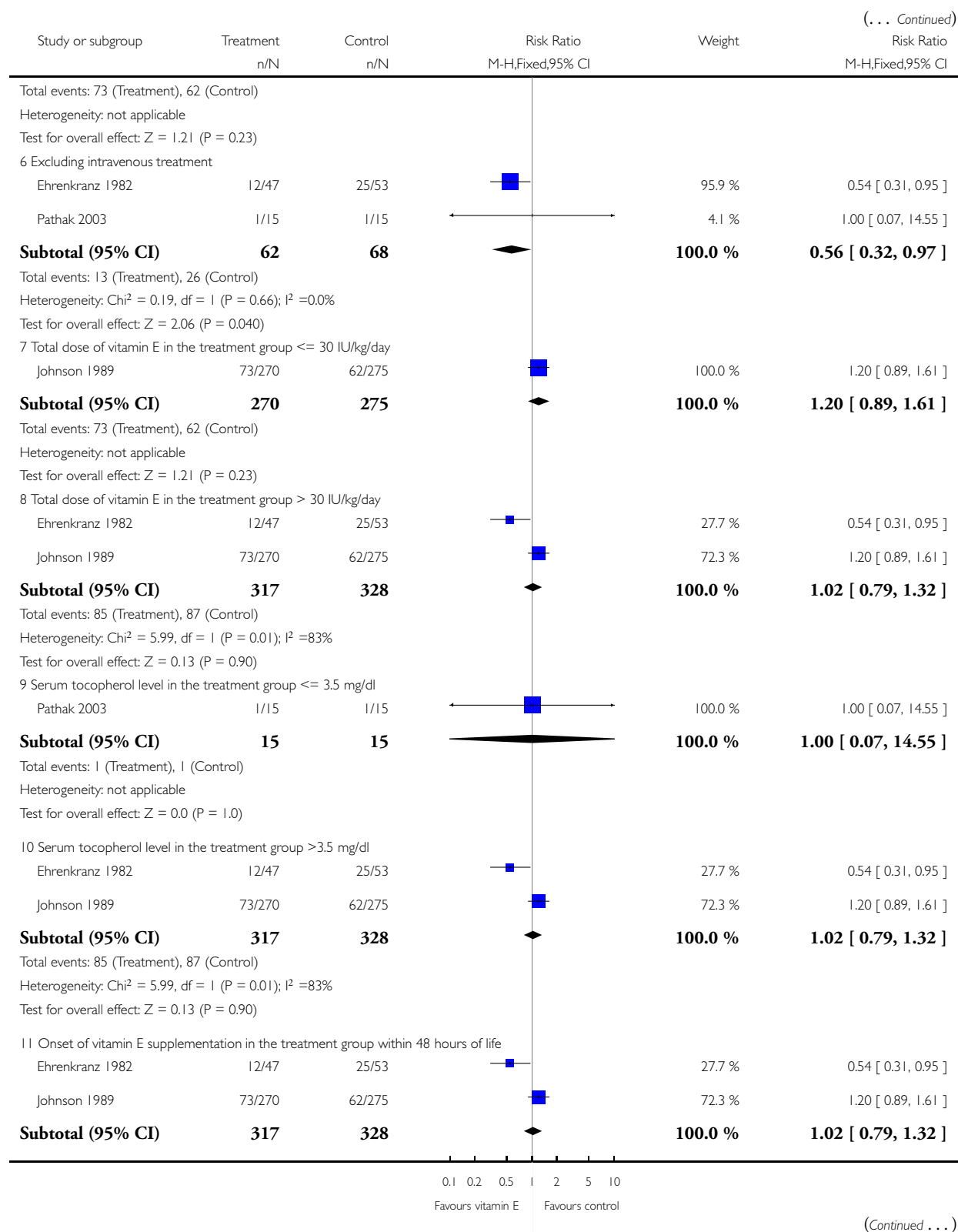
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

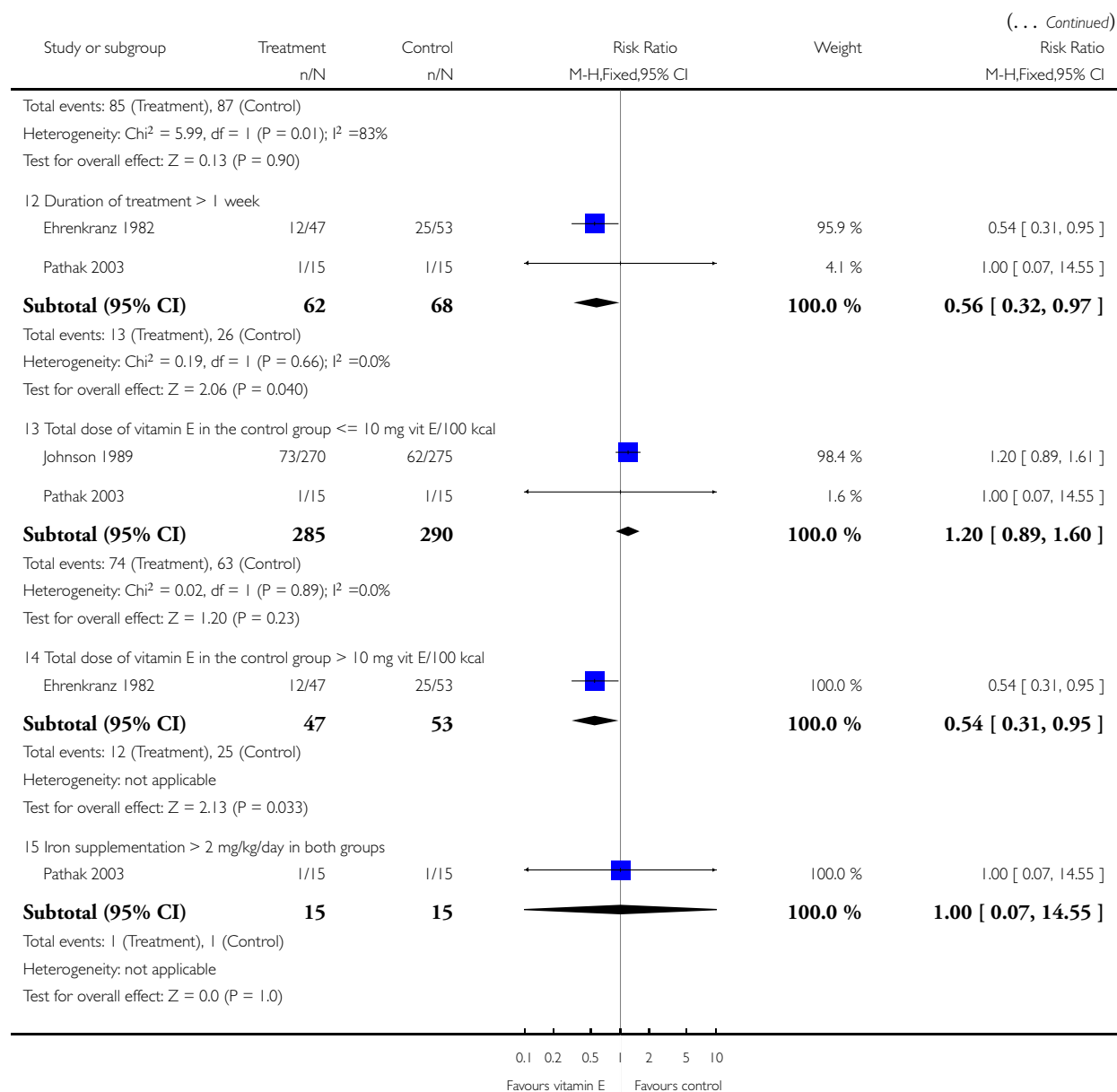
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 13 Patent ductus arteriosus requiring treatment



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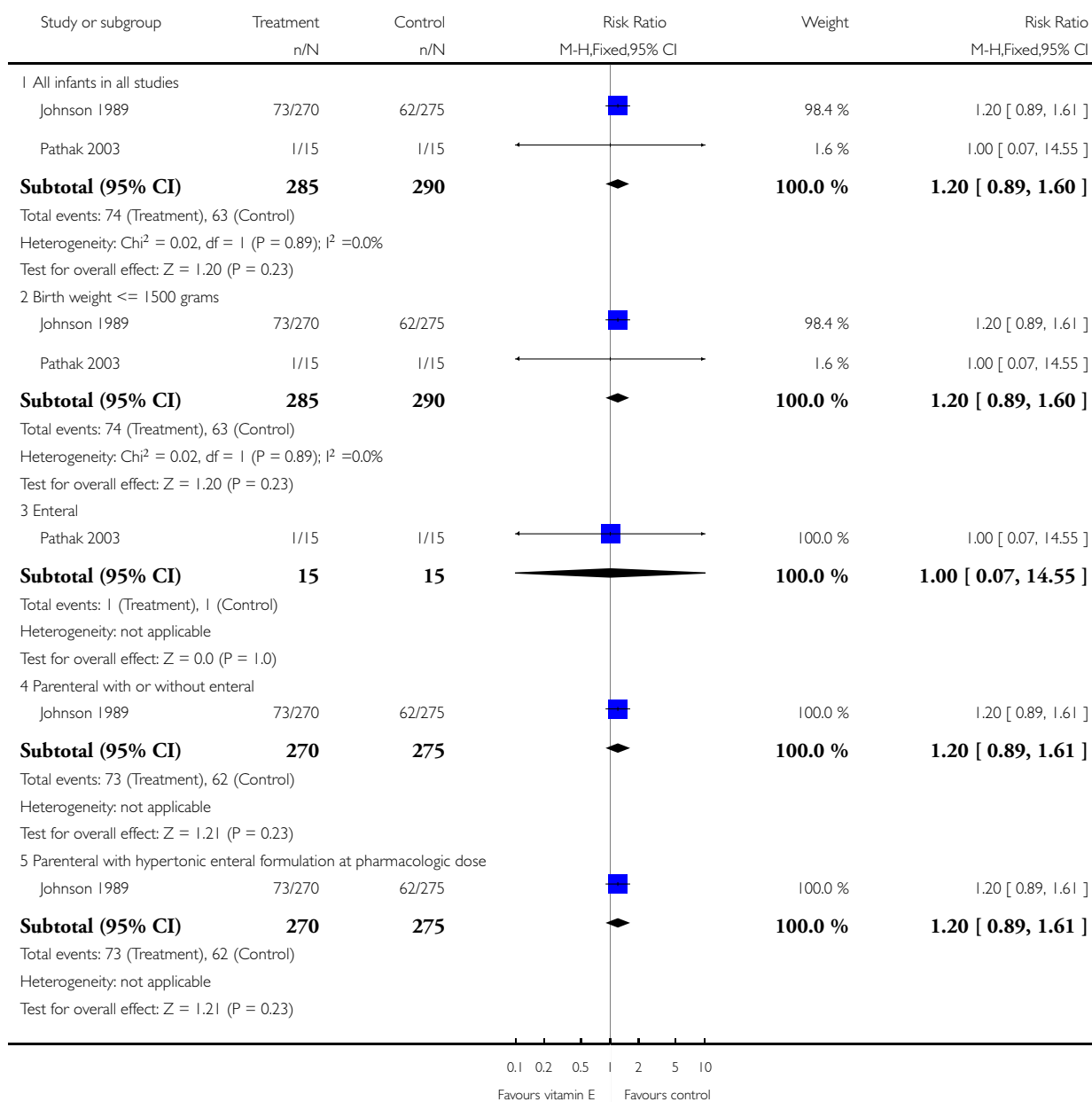


# **Analysis 1.14. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 14 Patent ductus arteriosus requiring treatment among very low birth weight infants.**

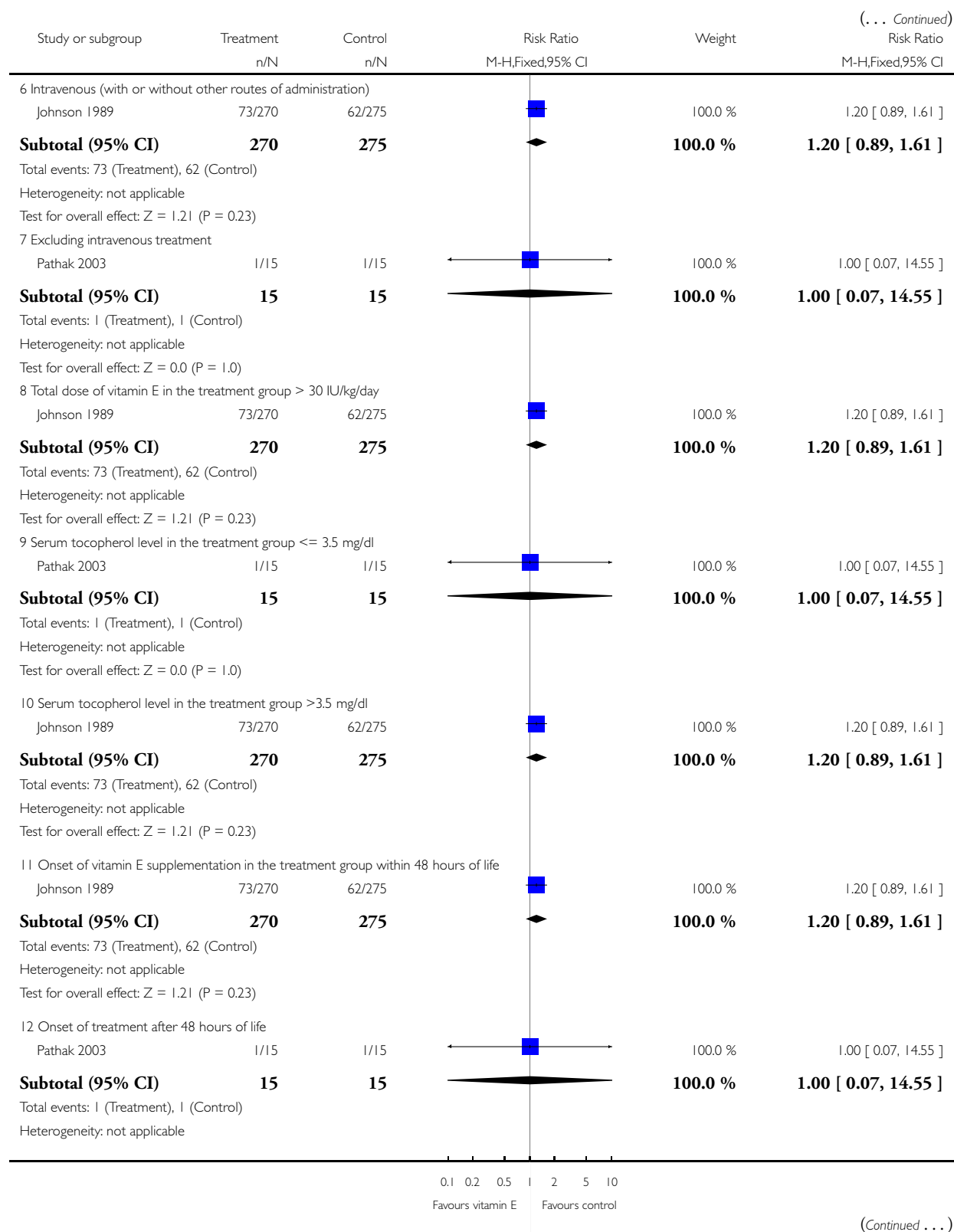
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

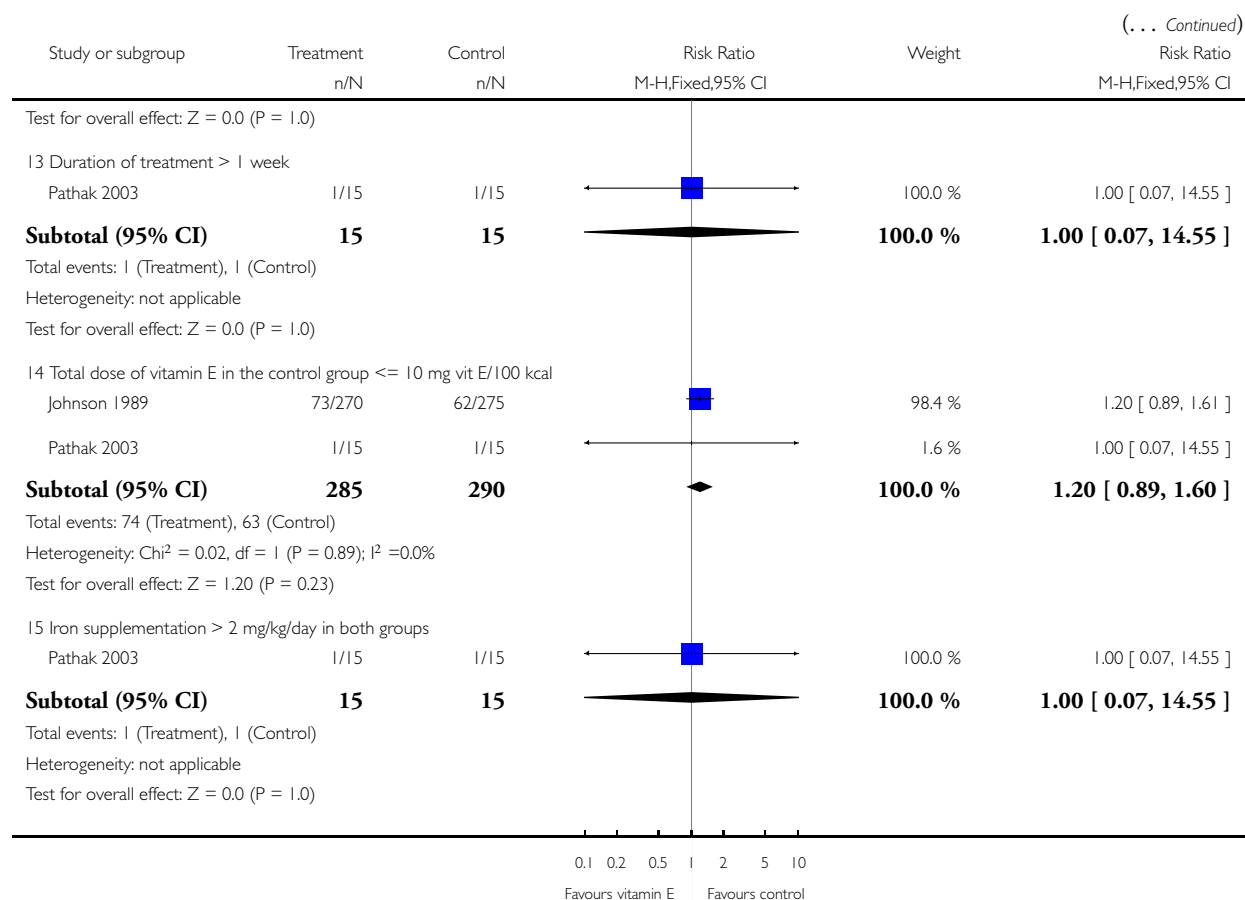
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 14 Patent ductus arteriosus requiring treatment among very low birth weight infants



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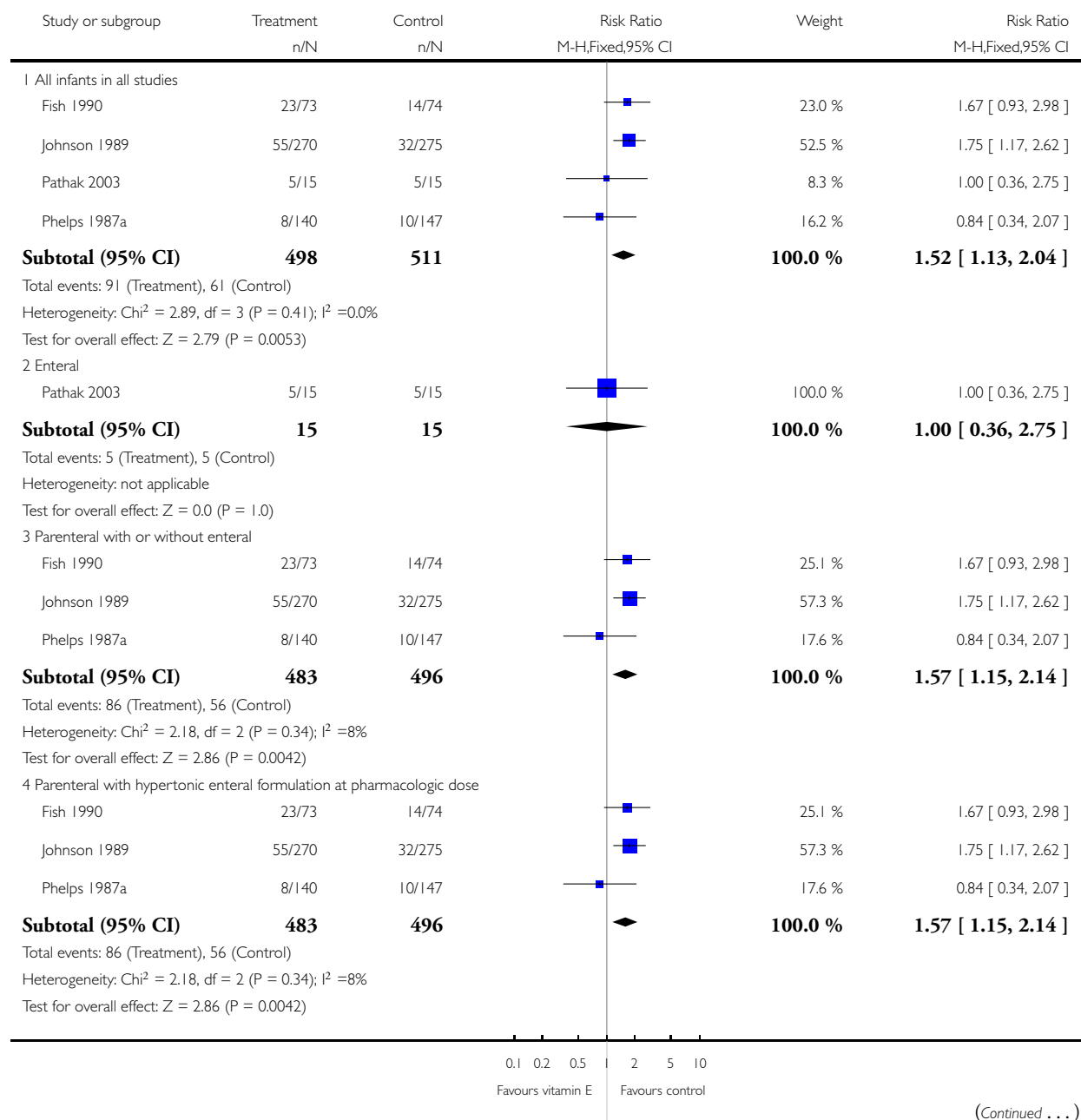


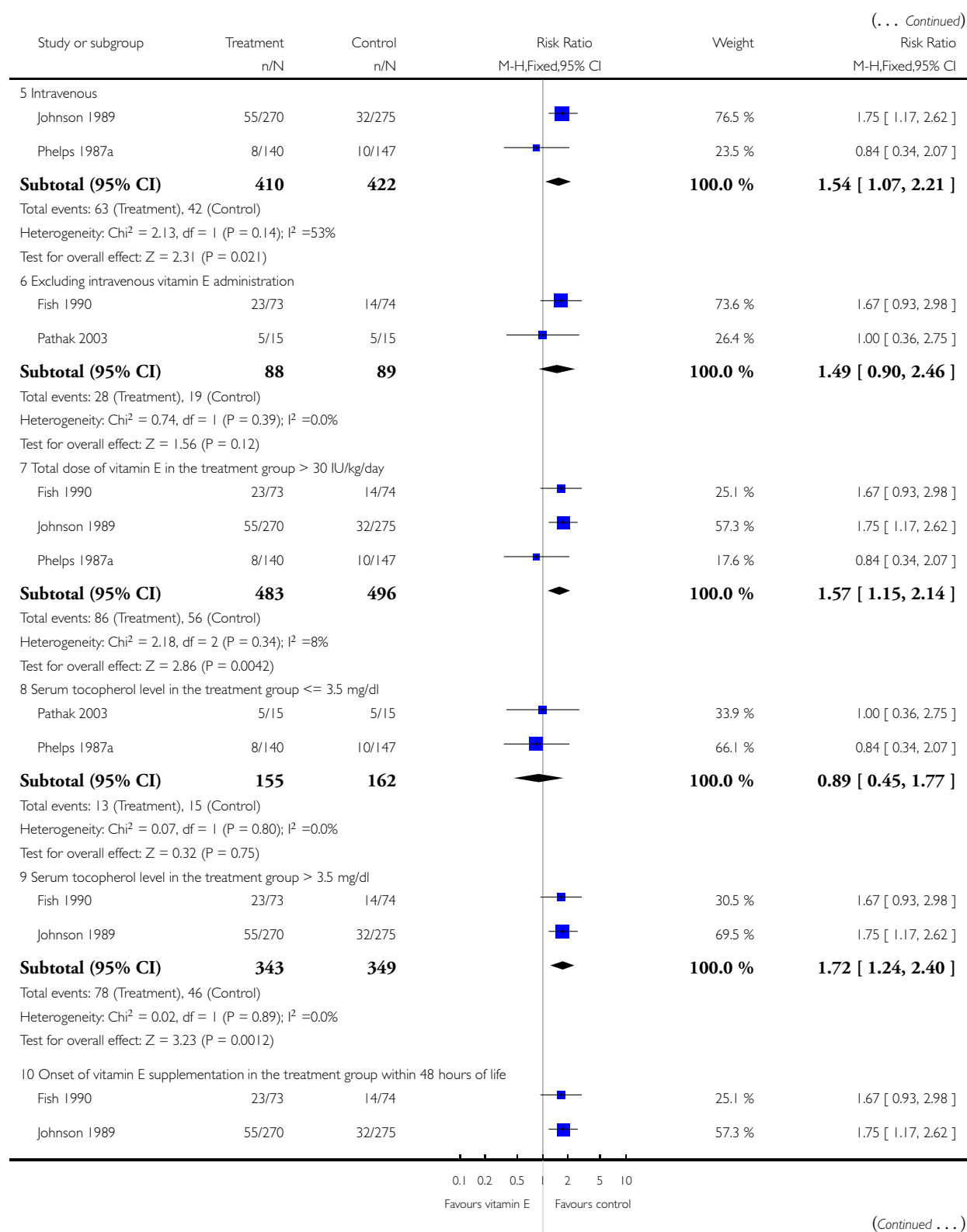
## Analysis 1.15. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 15 Sepsis after study entry.

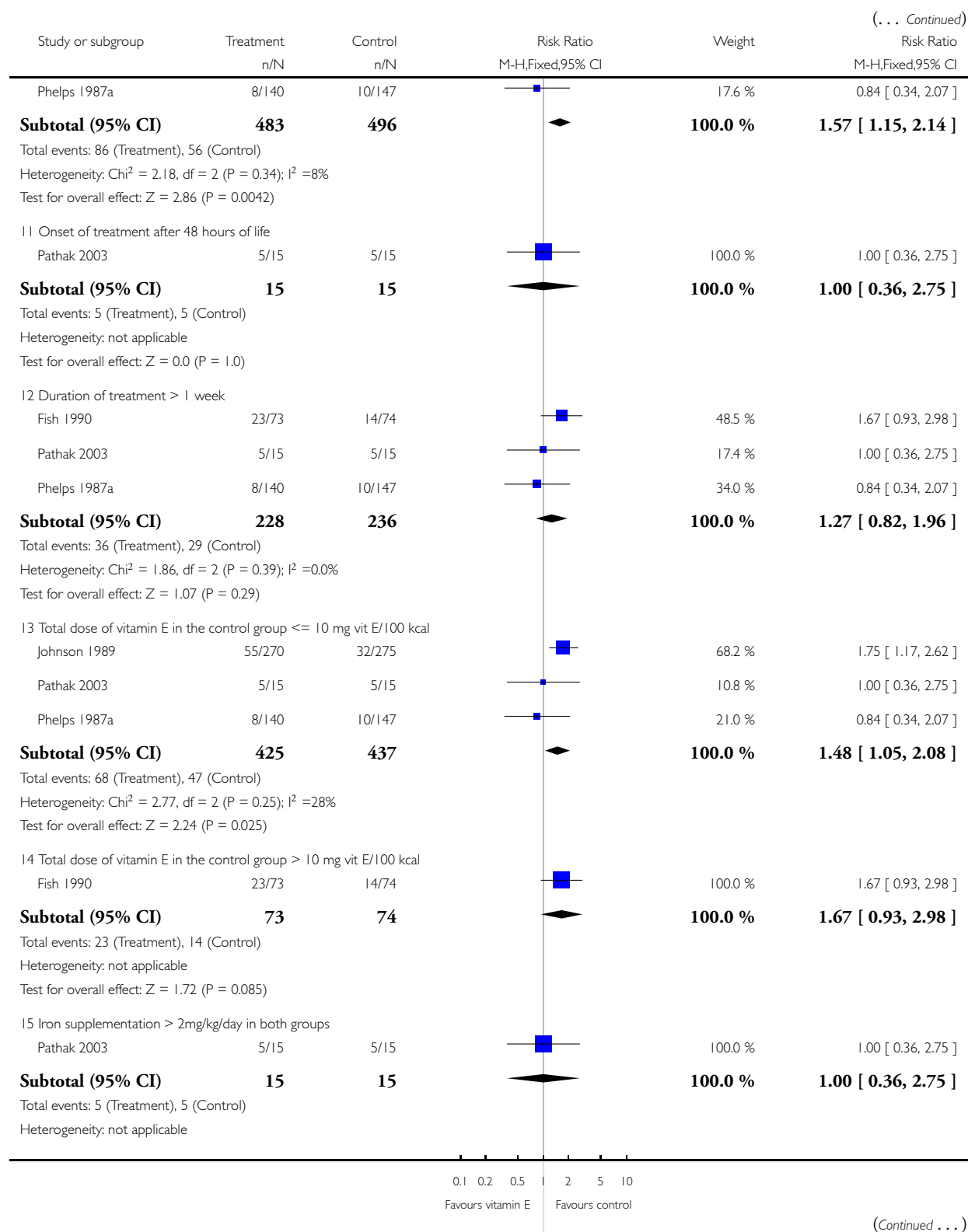
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 15 Sepsis after study entry







(... Continued)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.0 (P = 1.0)					
<div> <div>0.10.20.5</div> <div>Favours vitamin E</div> <div>2510</div> <div>Favours control</div> </div>					

### Analysis 1.16. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 16 Sepsis after study entry among very low birth weight infants.

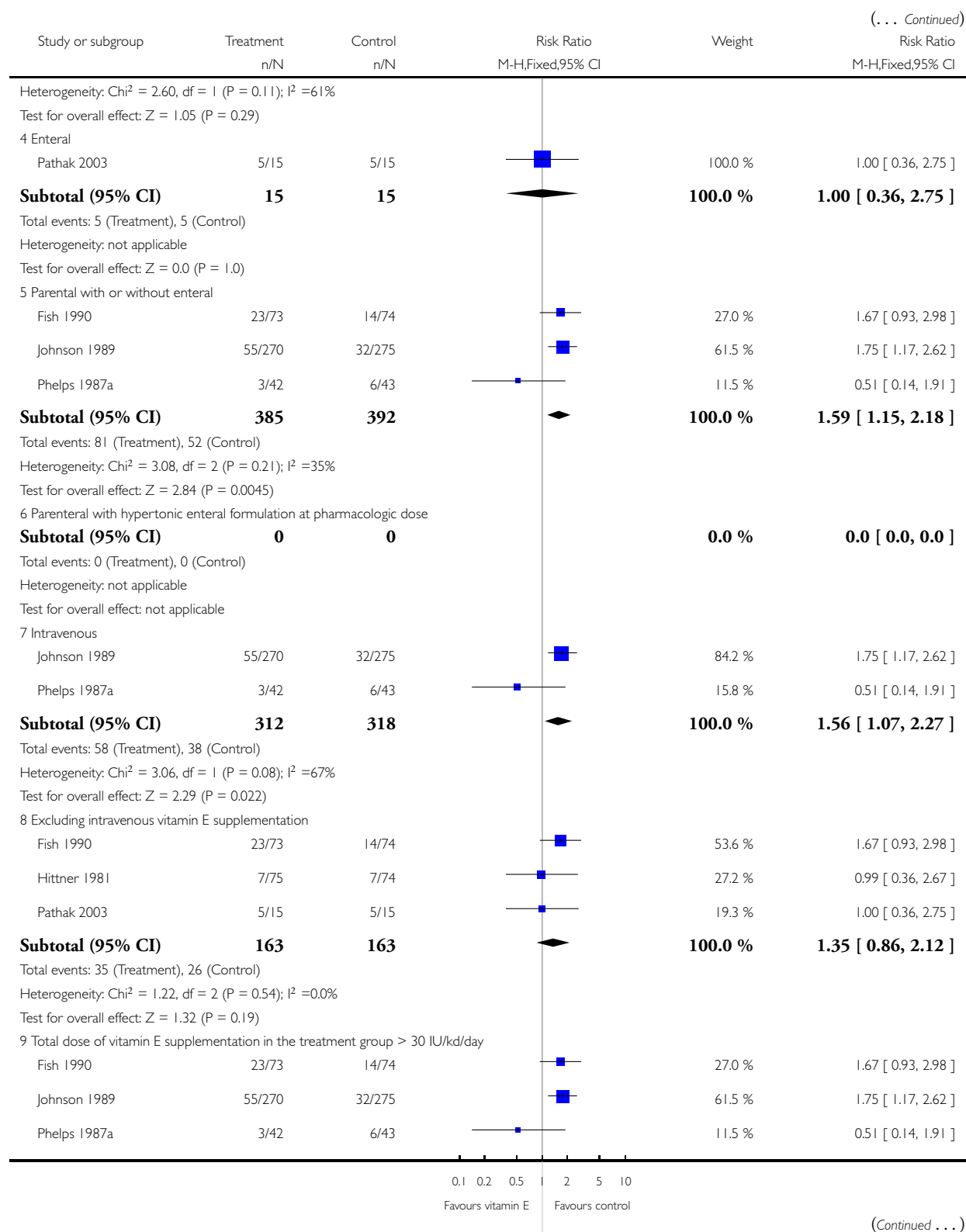
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

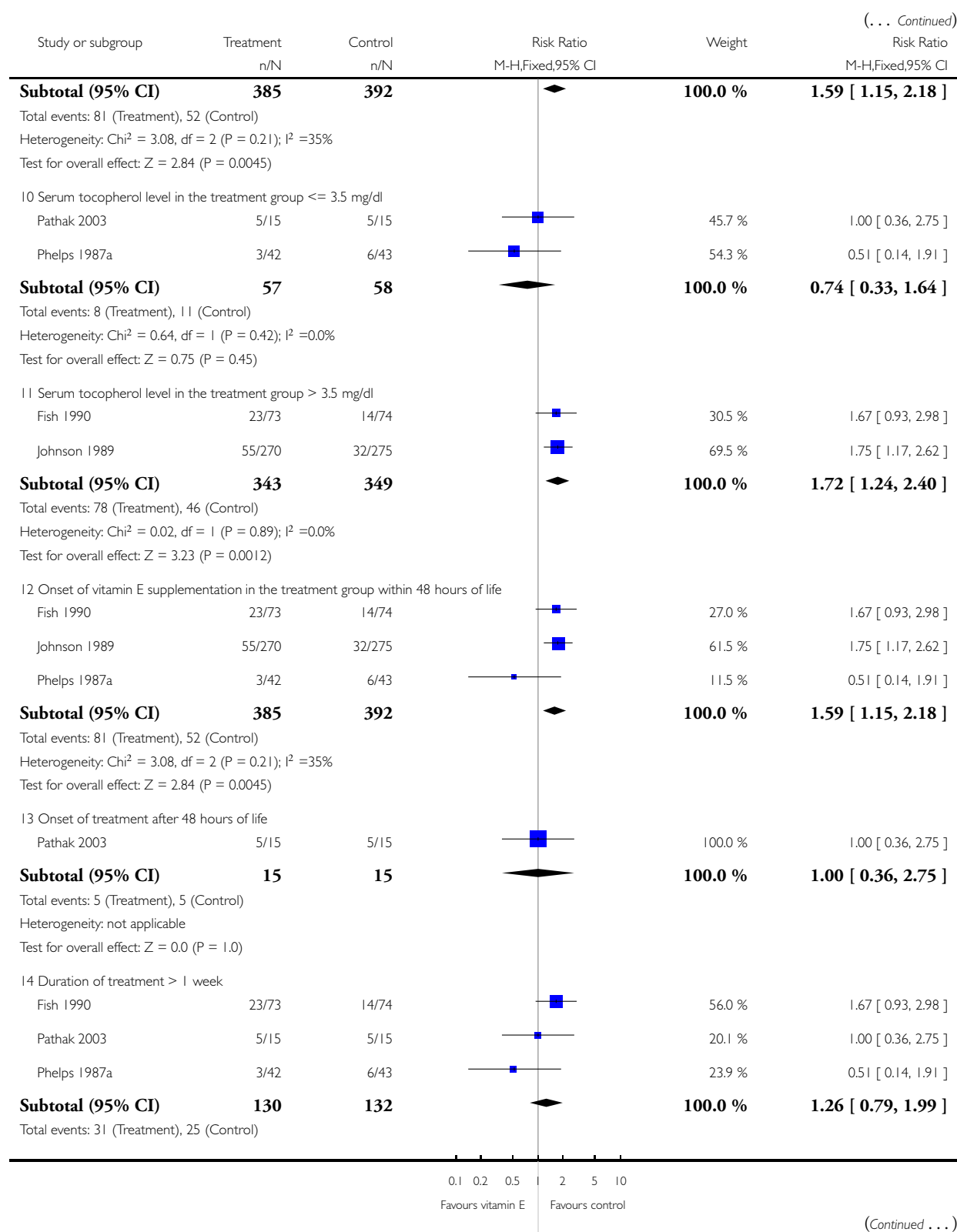
Comparison: 1 Vitamin E versus placebo or no vitamin E

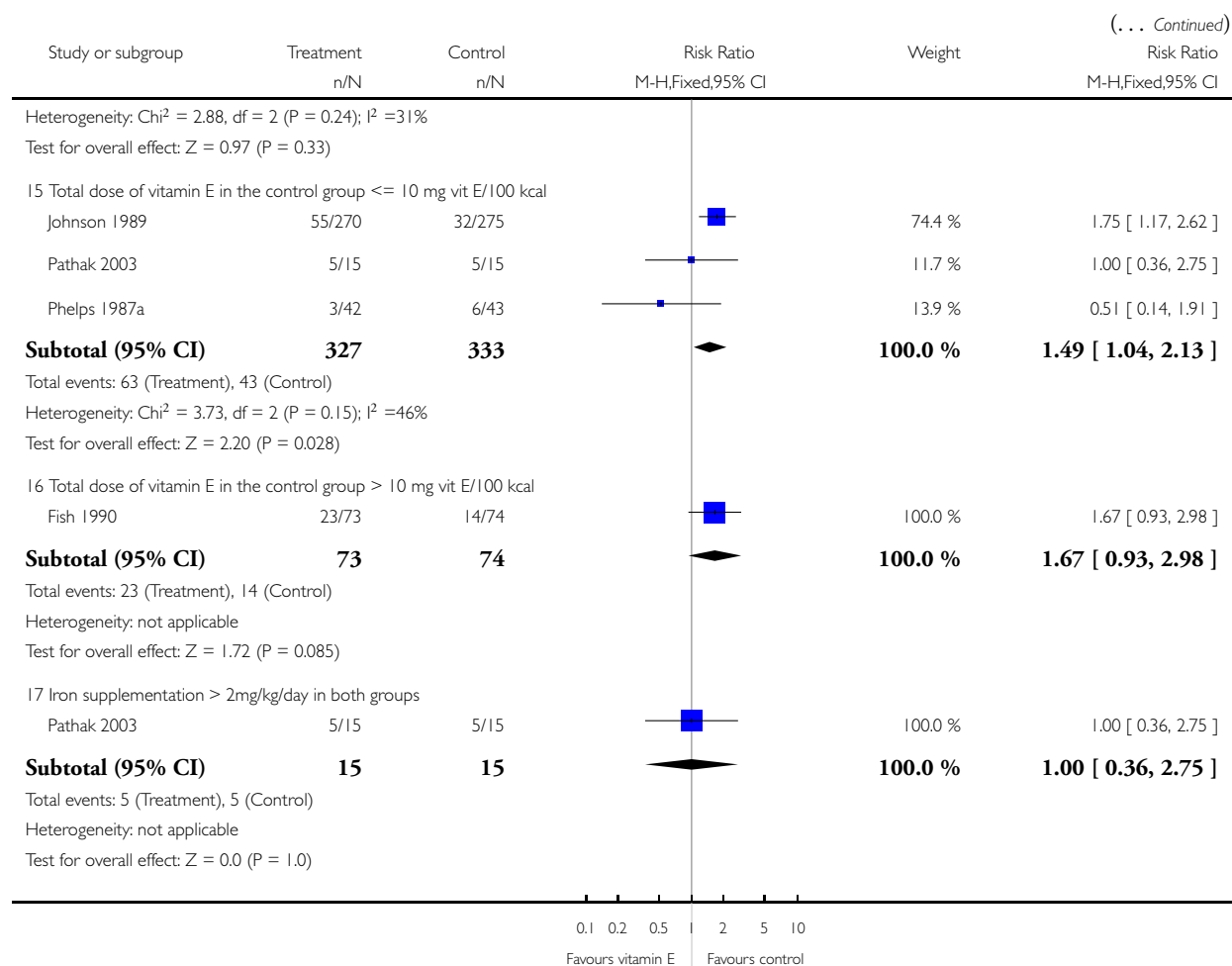
Outcome: 16 Sepsis after study entry among very low birth weight infants

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
I All infants in all studies					
Fish 1990	23/73	14/74		24.6 %	1.67 [ 0.93, 2.98 ]
Johnson 1989	55/270	32/275		56.1 %	1.75 [ 1.17, 2.62 ]
Pathak 2003	5/15	5/15		8.8 %	1.00 [ 0.36, 2.75 ]
Phelps 1987a	3/42	6/43		10.5 %	0.51 [ 0.14, 1.91 ]
<b>Subtotal (95% CI)</b>	<b>400</b>	<b>407</b>		<b>100.0 %</b>	<b>1.53 [ 1.13, 2.08 ]</b>
Total events: 86 (Treatment), 57 (Control)					
Heterogeneity: Chi <sup>2</sup> = 3.84, df = 3 (P = 0.28); I <sup>2</sup> = 22%					
Test for overall effect: Z = 2.77 (P = 0.0057)					
2 Birth weight <= 1500 grams					
Johnson 1989	55/270	32/275		86.4 %	1.75 [ 1.17, 2.62 ]
Pathak 2003	5/15	5/15		13.6 %	1.00 [ 0.36, 2.75 ]
<b>Subtotal (95% CI)</b>	<b>285</b>	<b>290</b>		<b>100.0 %</b>	<b>1.65 [ 1.13, 2.40 ]</b>
Total events: 60 (Treatment), 37 (Control)					
Heterogeneity: Chi <sup>2</sup> = 1.02, df = 1 (P = 0.31); I <sup>2</sup> = 2%					
Test for overall effect: Z = 2.62 (P = 0.0088)					
3 Birth weight <= 1000 grams					
Fish 1990	23/73	14/74		70.1 %	1.67 [ 0.93, 2.98 ]
Phelps 1987a	3/42	6/43		29.9 %	0.51 [ 0.14, 1.91 ]
<b>Subtotal (95% CI)</b>	<b>115</b>	<b>117</b>		<b>100.0 %</b>	<b>1.32 [ 0.79, 2.22 ]</b>
Total events: 26 (Treatment), 20 (Control)					
<div> <div>0.10.20.5</div> <div>Favours vitamin E</div> <div>2510</div> <div>Favours control</div> </div>					

(Continued ...)





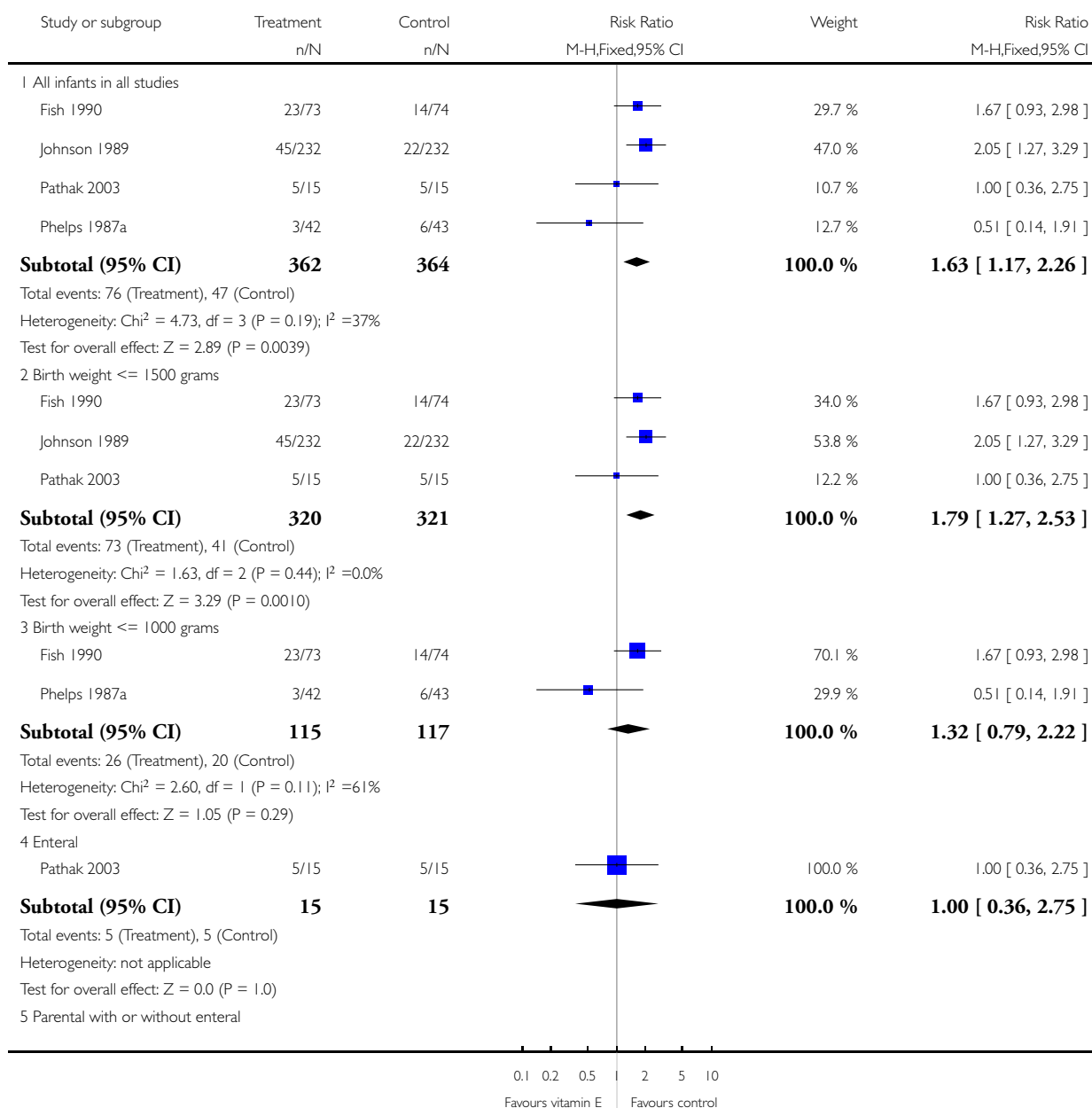


# **Analysis 1.17. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 17 Sepsis after study entry among very low birth weight infants treated for > 1 week.**

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

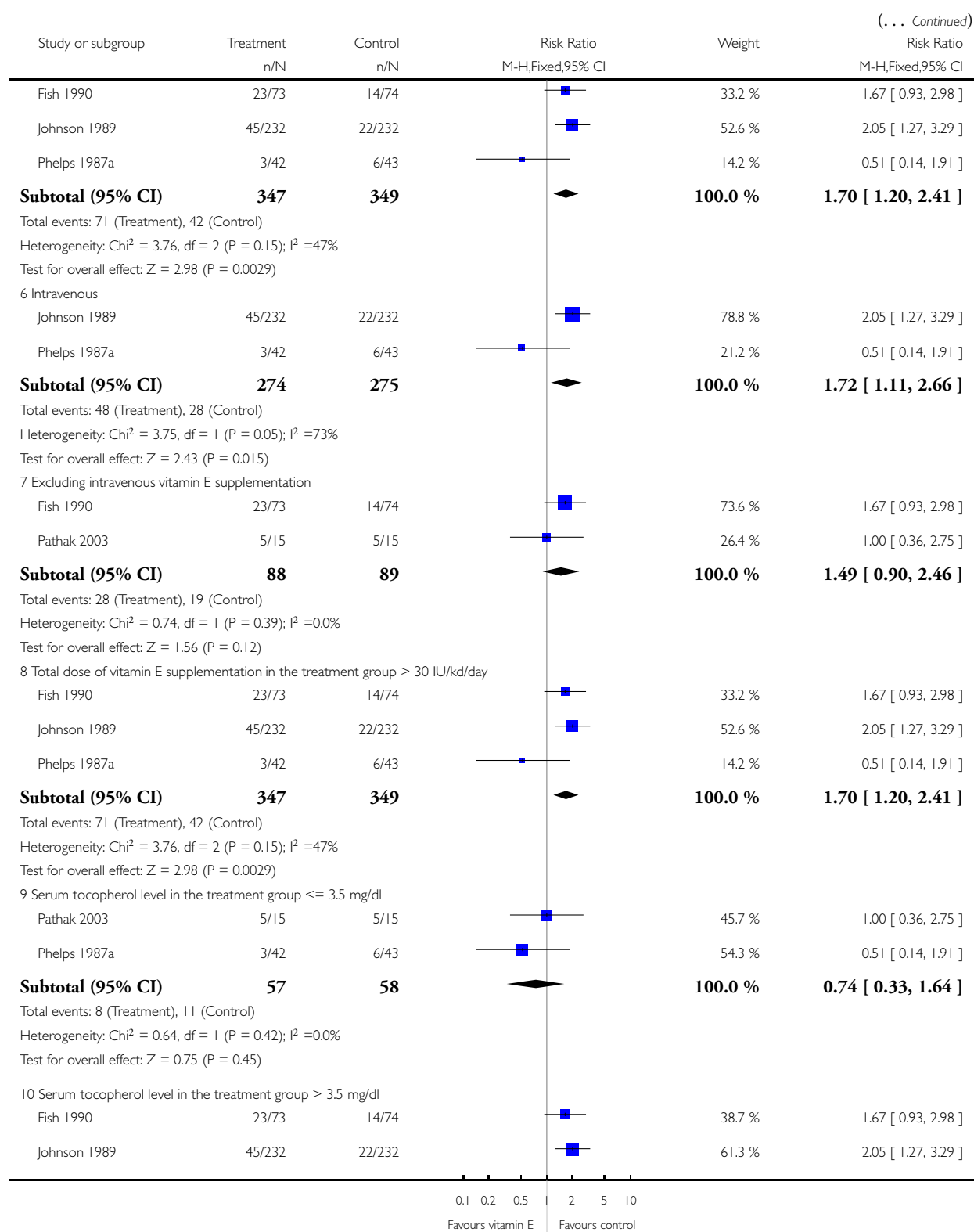
Comparison: 1 Vitamin E versus placebo or no vitamin E

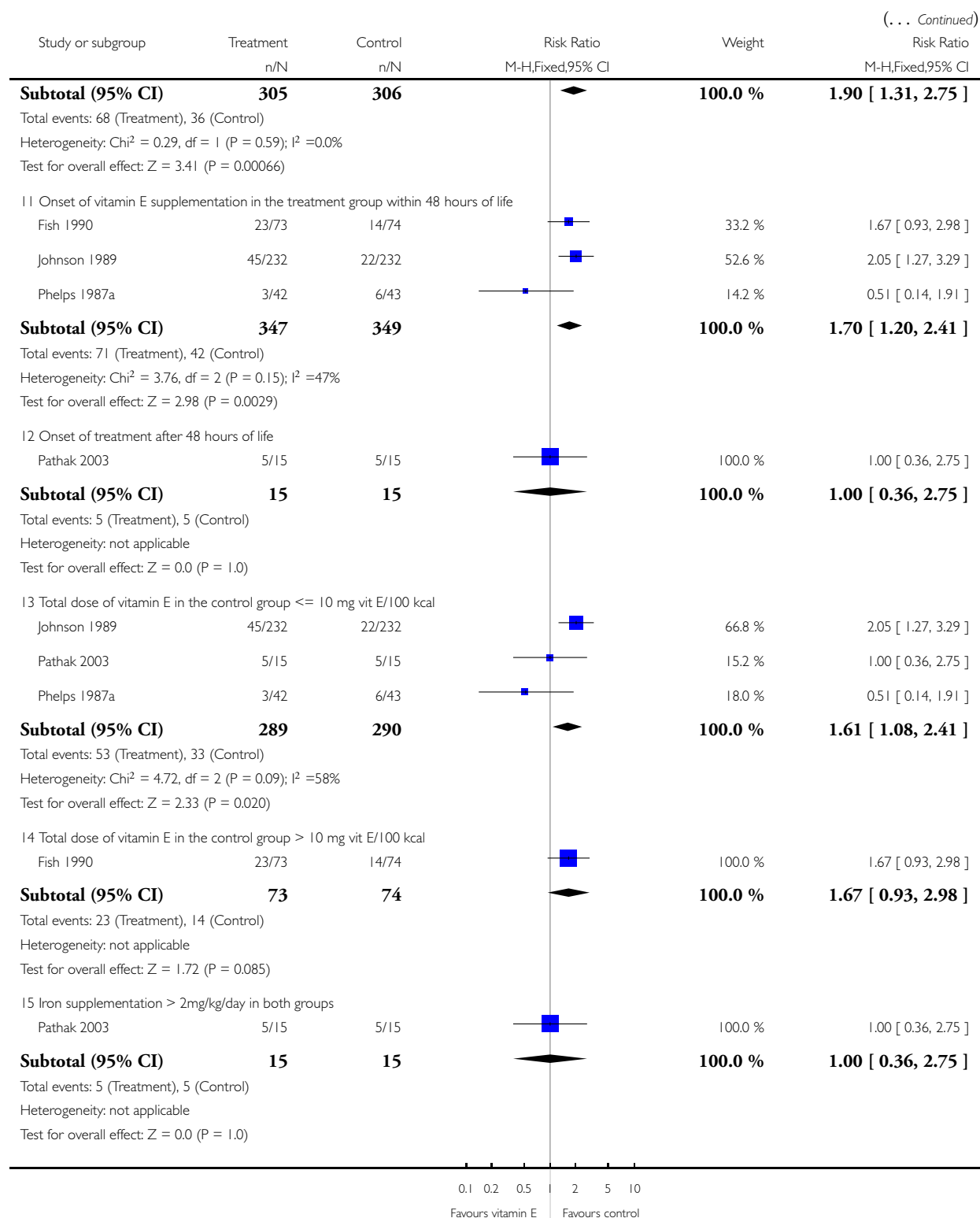
Outcome: 17 Sepsis after study entry among very low birth weight infants treated for > 1 week



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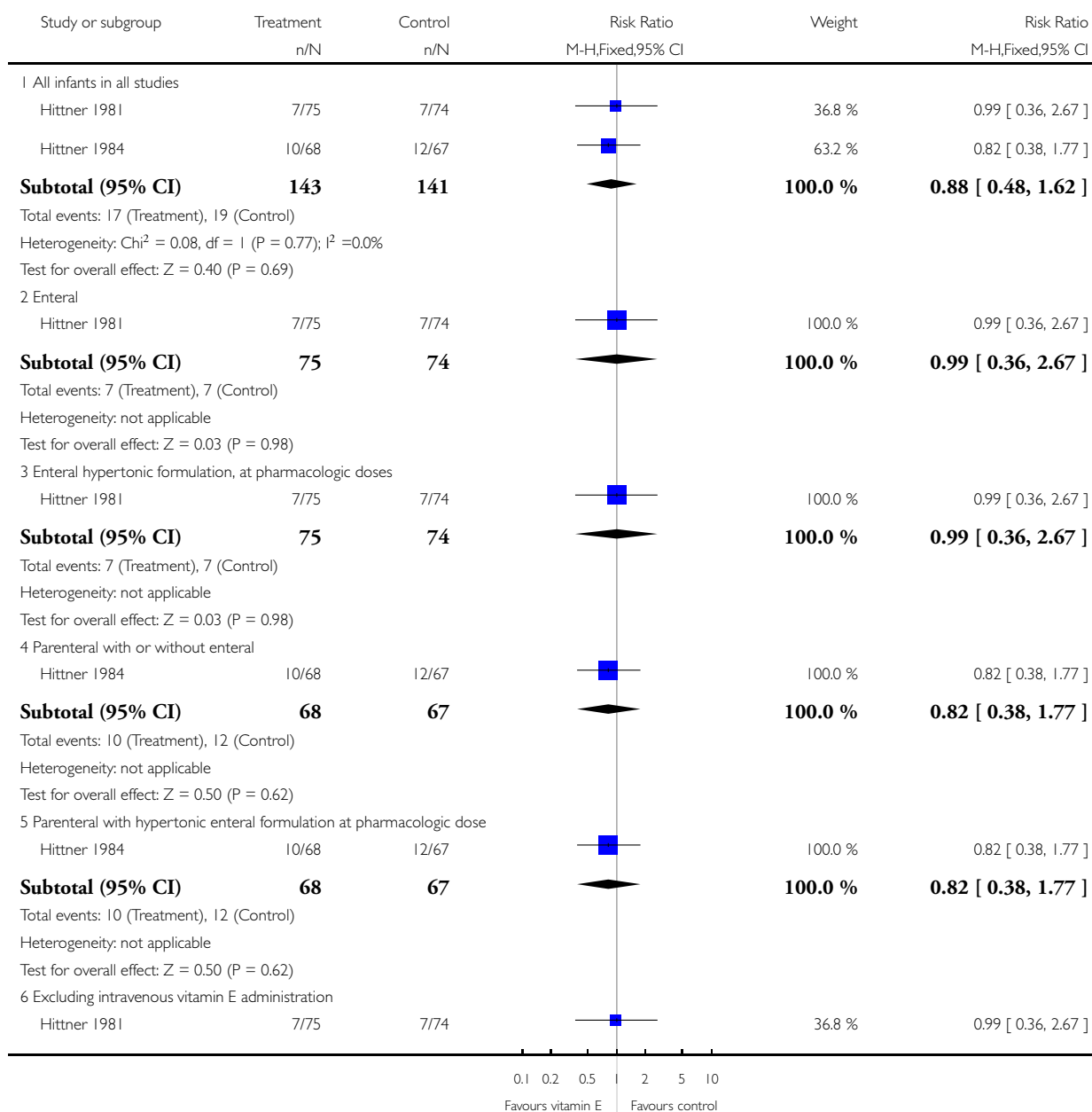


# **Analysis 1.18. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 18 Sepsis among surviving very low birth weight infants.**

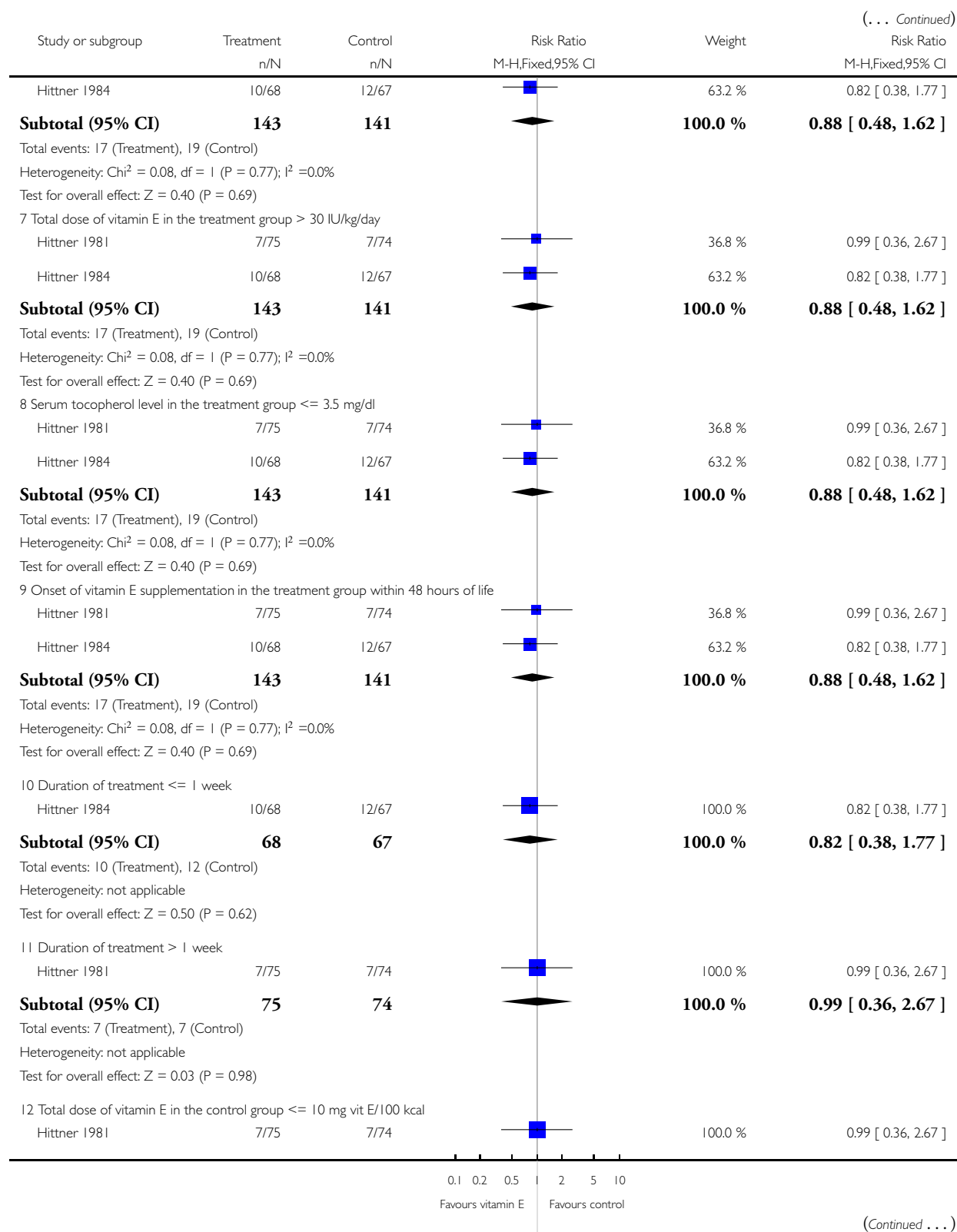
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

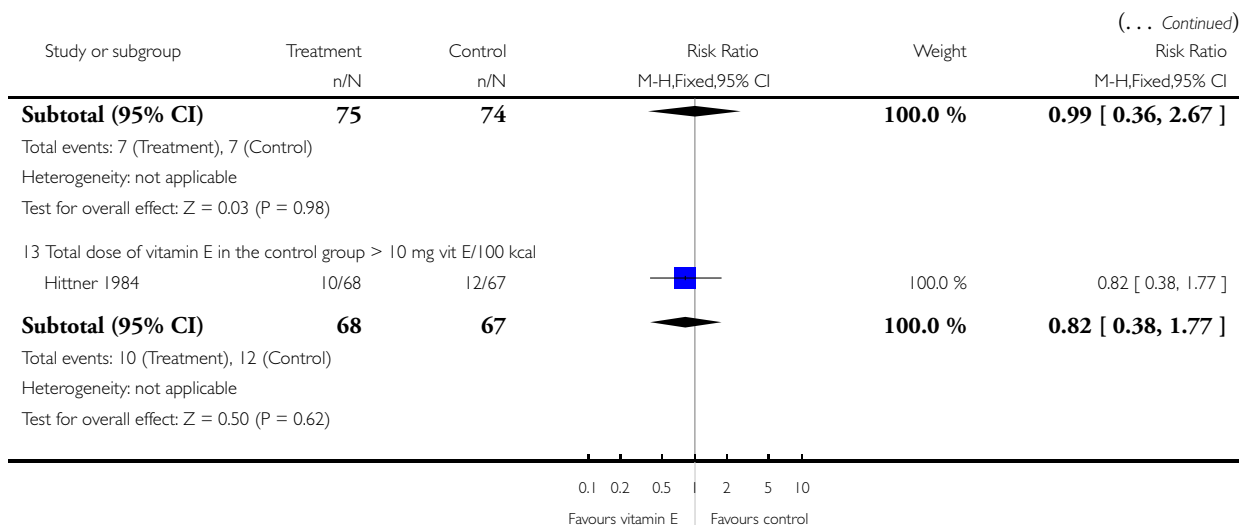
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 18 Sepsis among surviving very low birth weight infants



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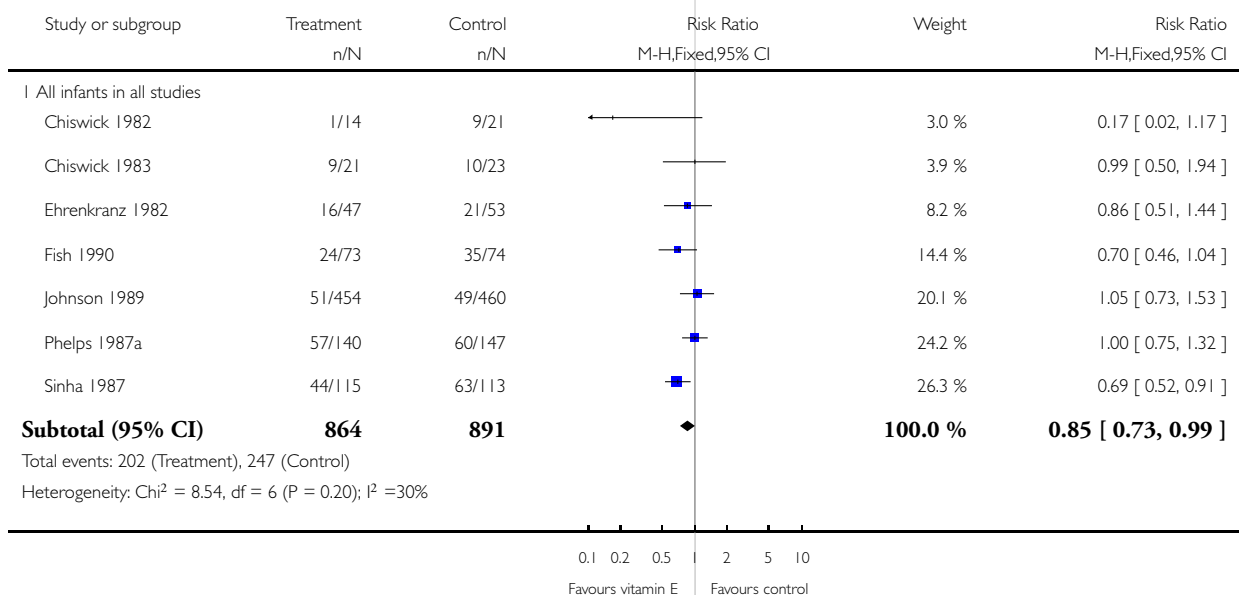


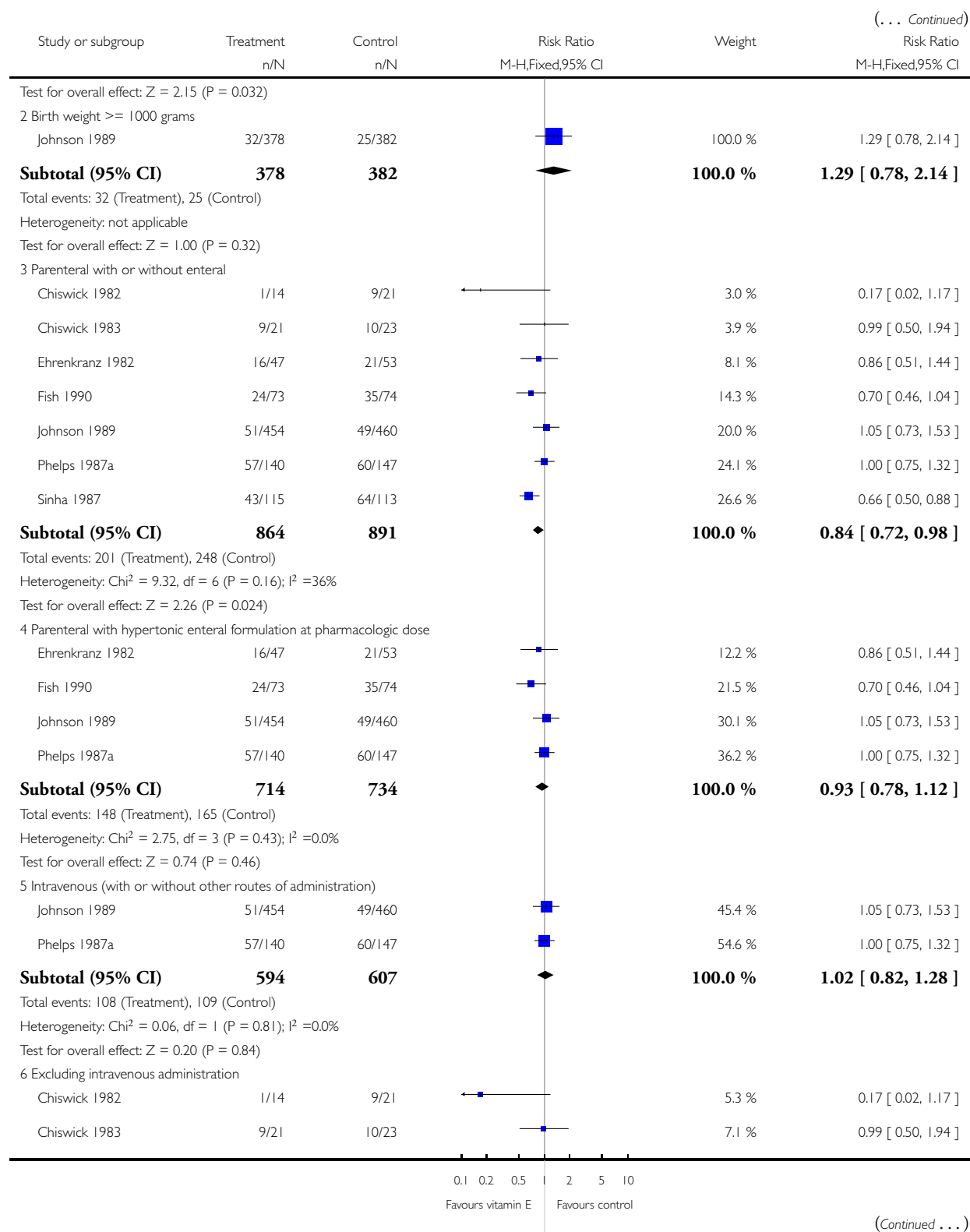
### Analysis 1.19. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 19 Germinal matrix/intraventricular hemorrhage (grades I-IV).

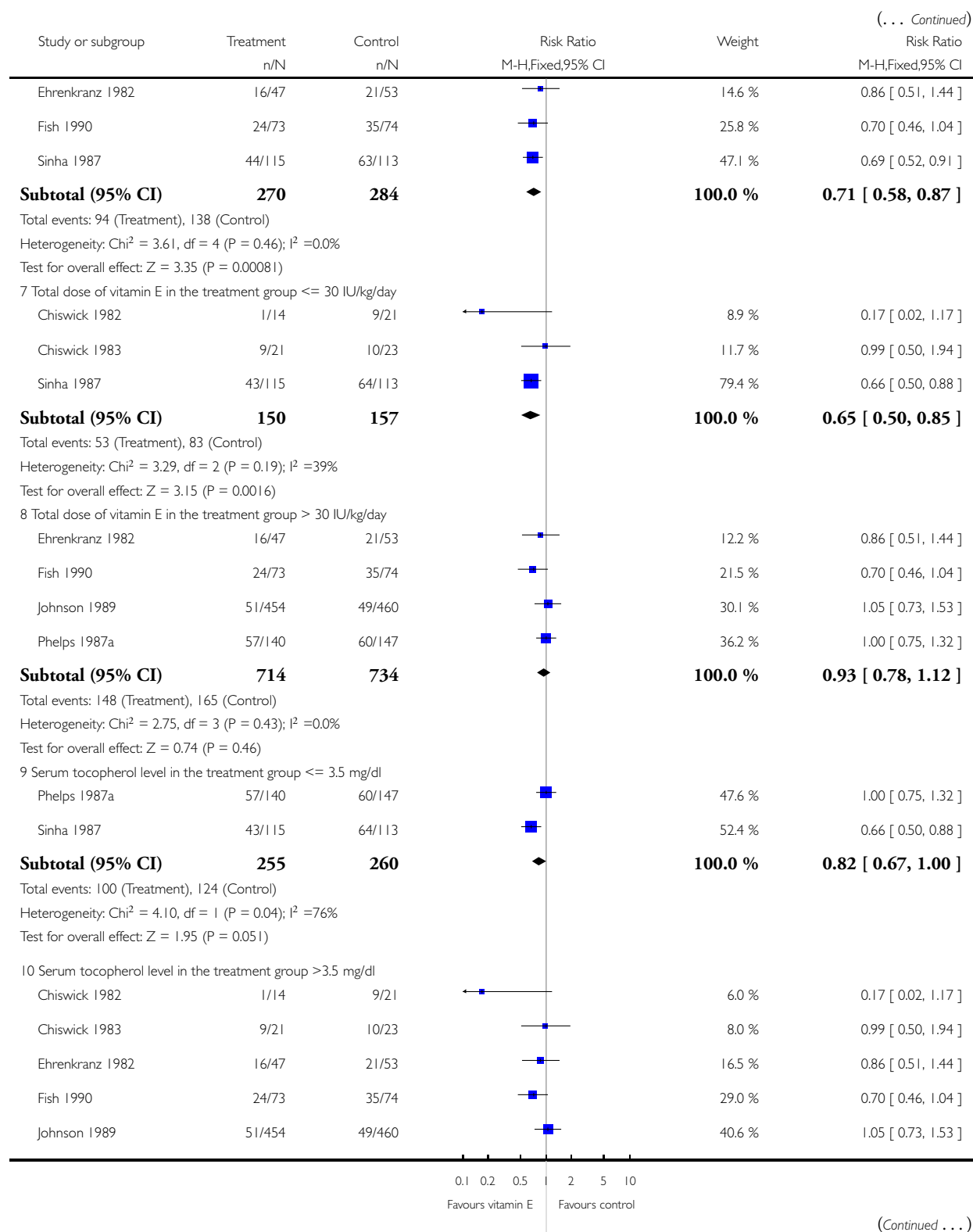
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

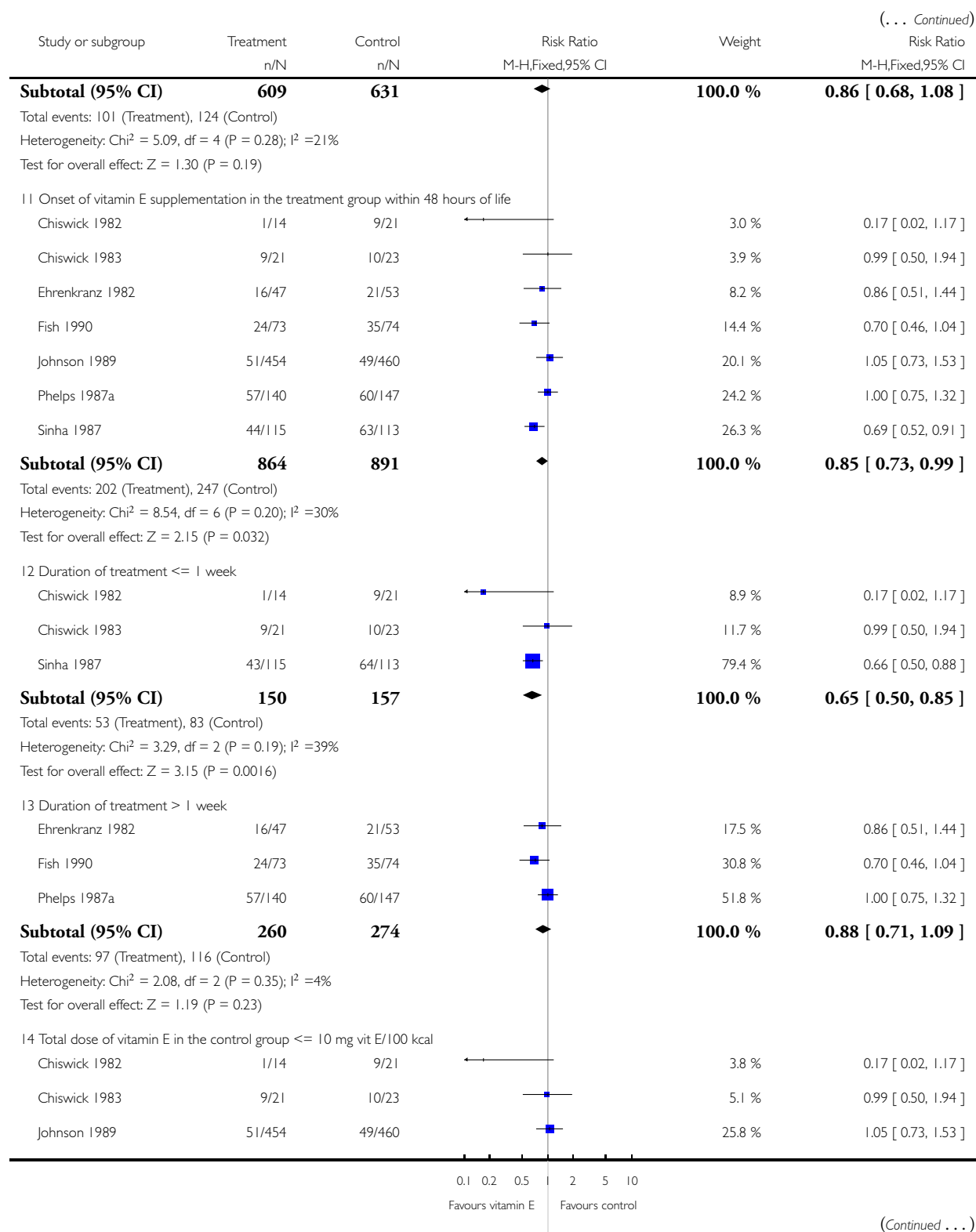
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 19 Germinal matrix/intraventricular hemorrhage (grades I-IV)

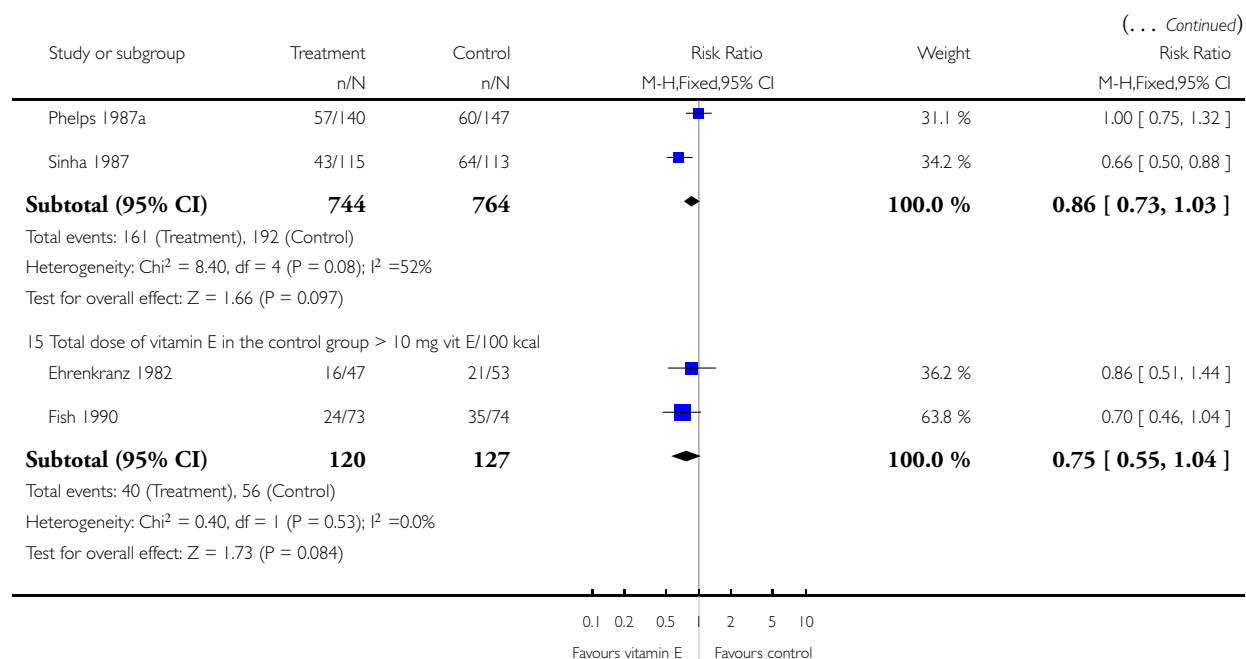










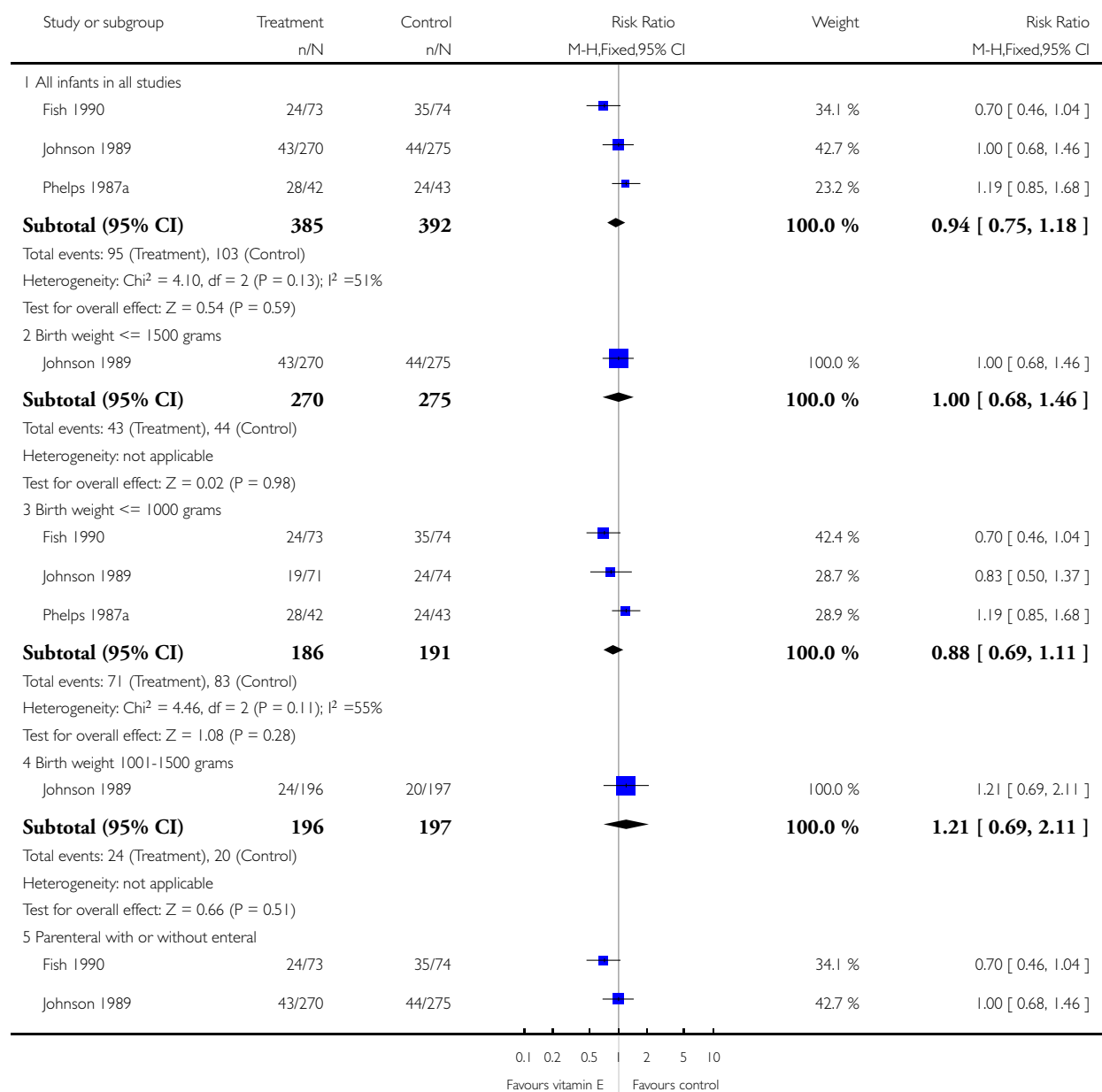


## Analysis 1.20. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 20 Germinal matrix/intraventricular hemorrhage among very low birth weight infants.

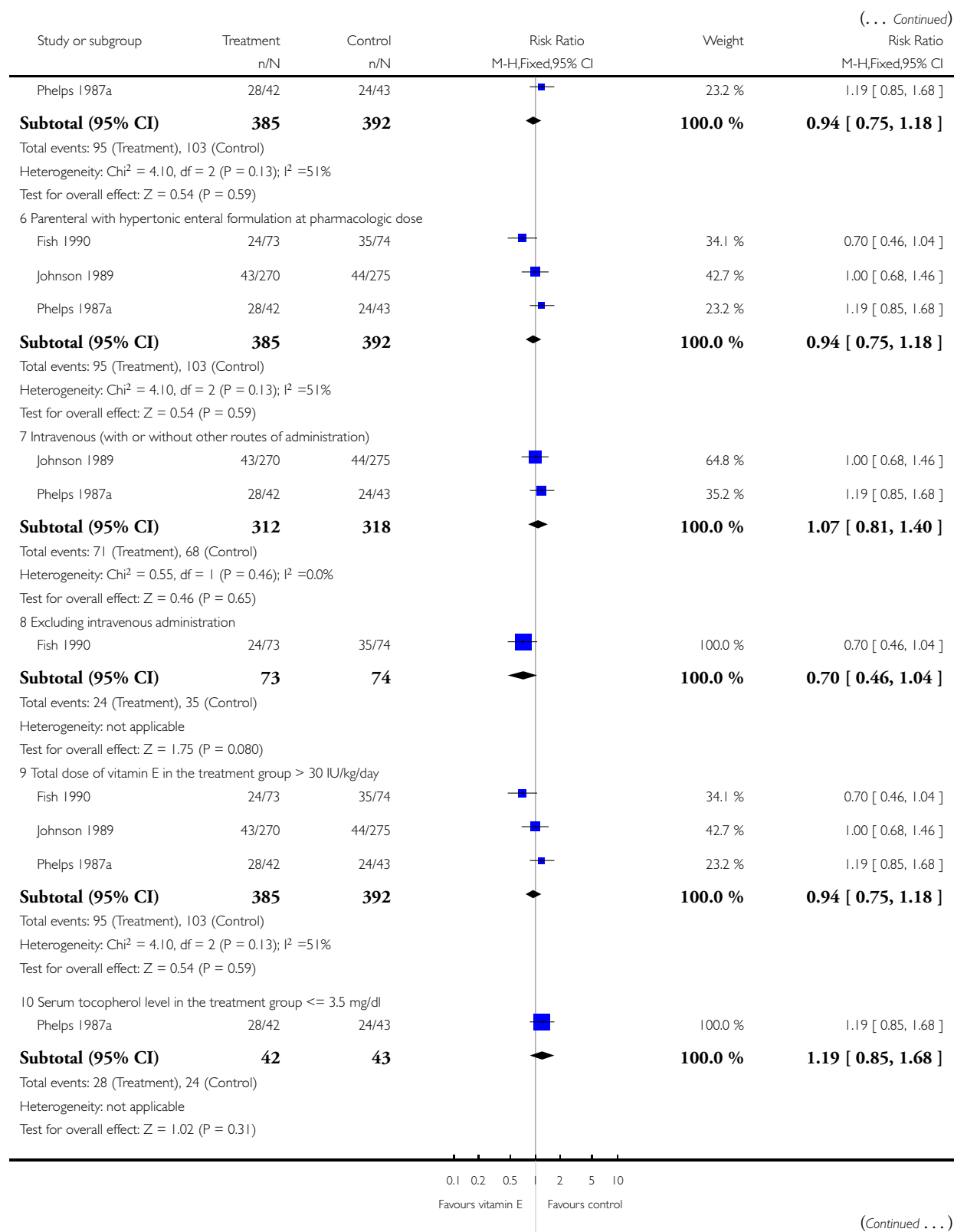
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

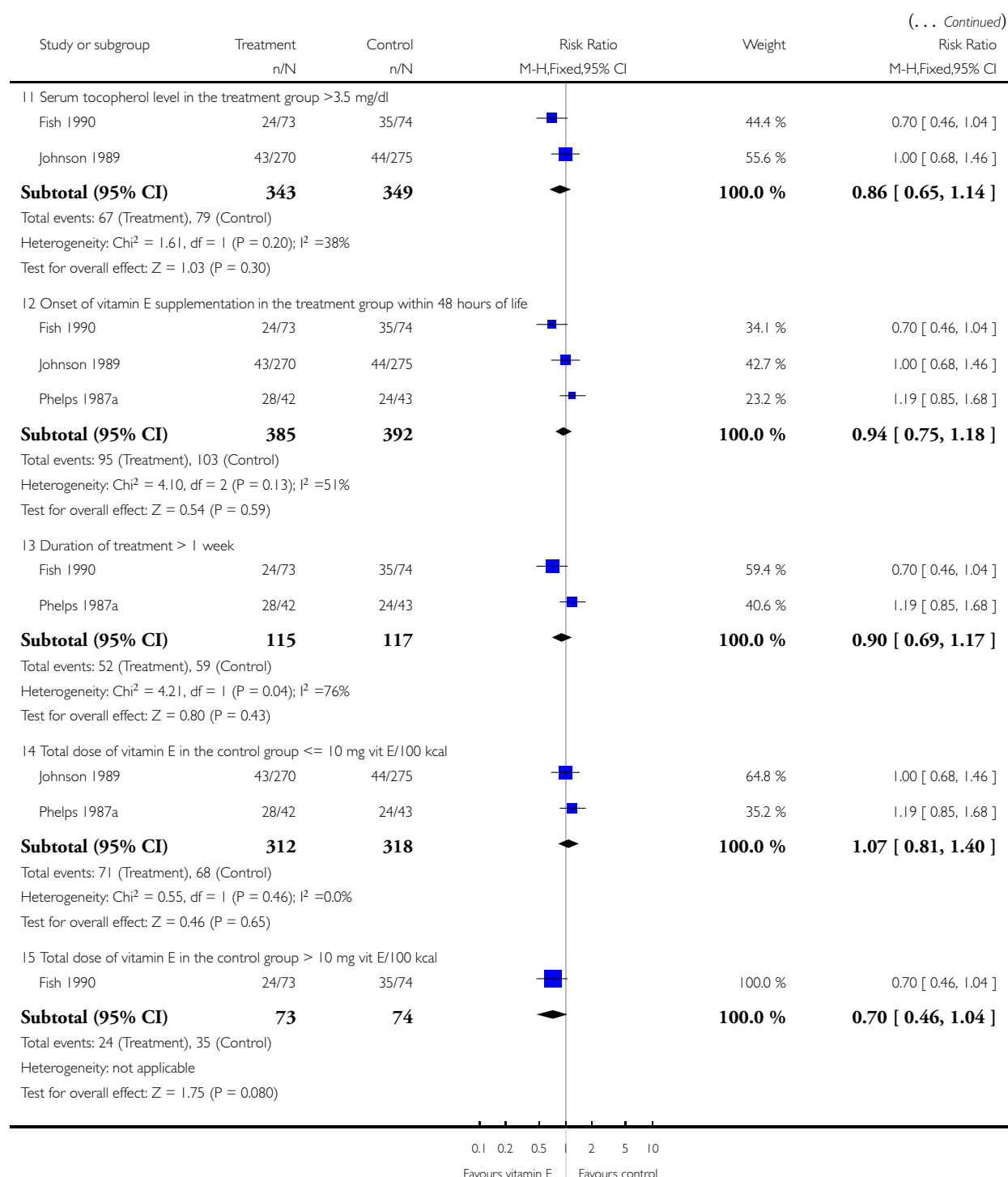
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 20 Germinal matrix/intraventricular hemorrhage among very low birth weight infants



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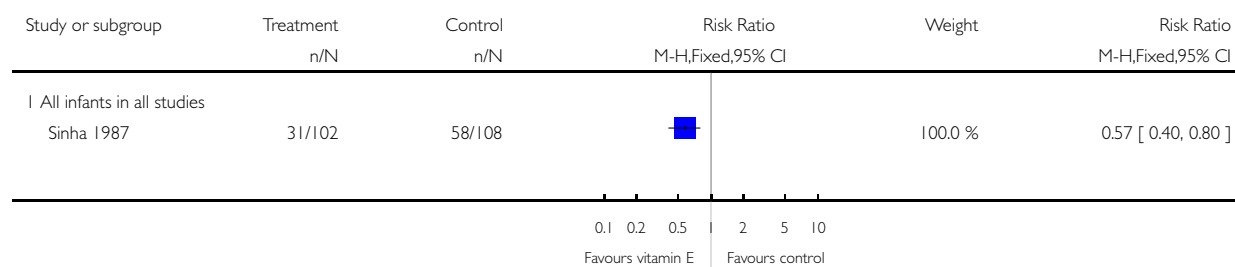


### Analysis 1.21. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 21 Germinal matrix/intraventricular hemorrhage among patients with negative initial ultrasonogram.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 21 Germinal matrix/intraventricular hemorrhage among patients with negative initial ultrasonogram

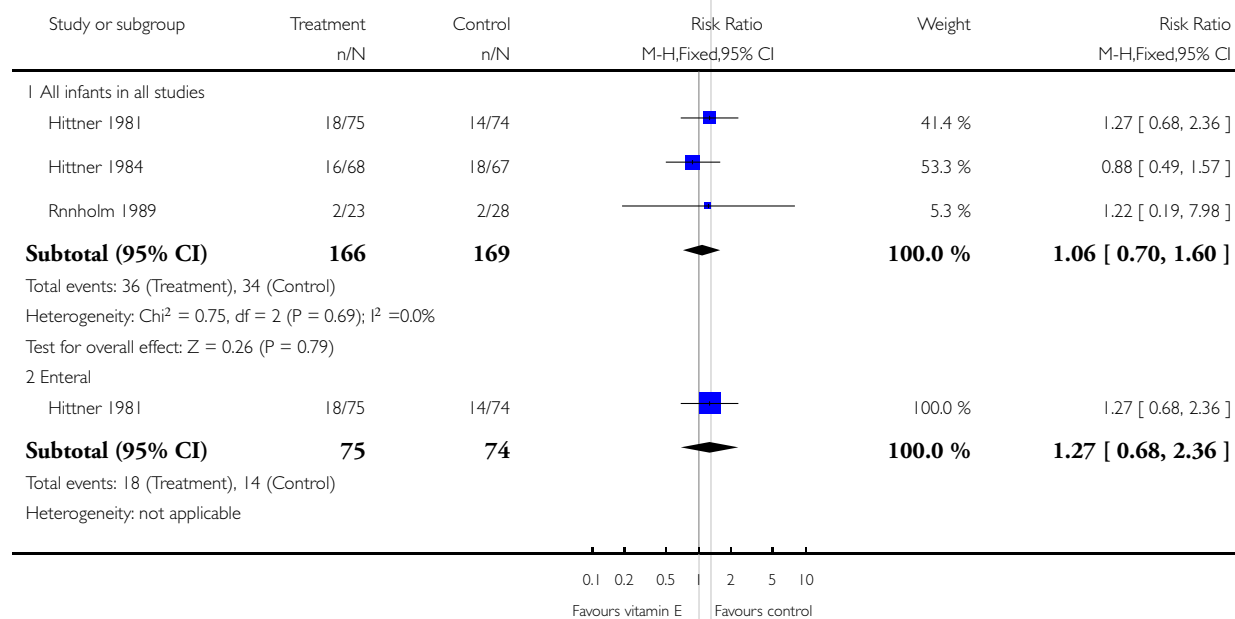


### Analysis 1.22. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 22 Germinal matrix/intraventricular hemorrhage among survivors.

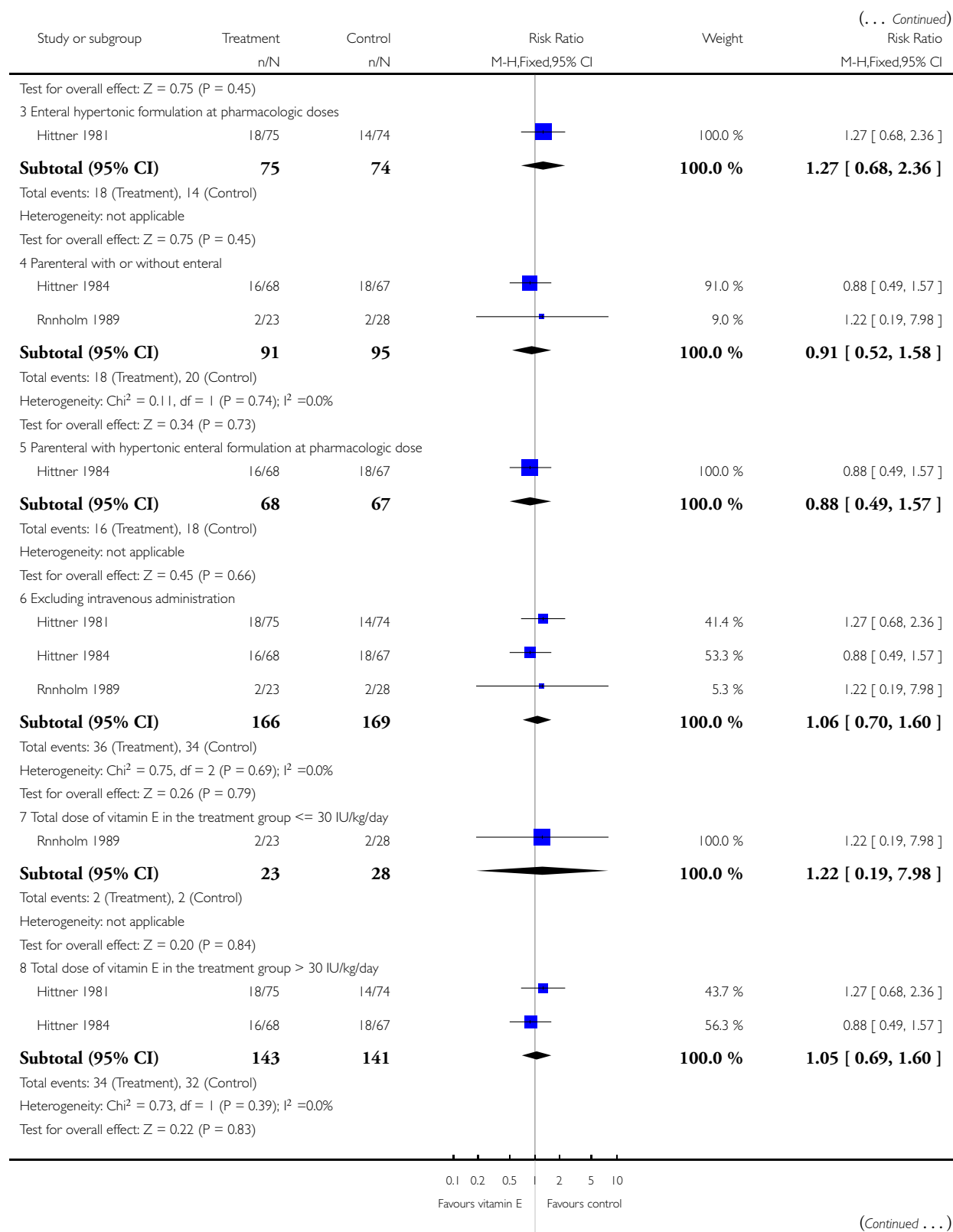
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

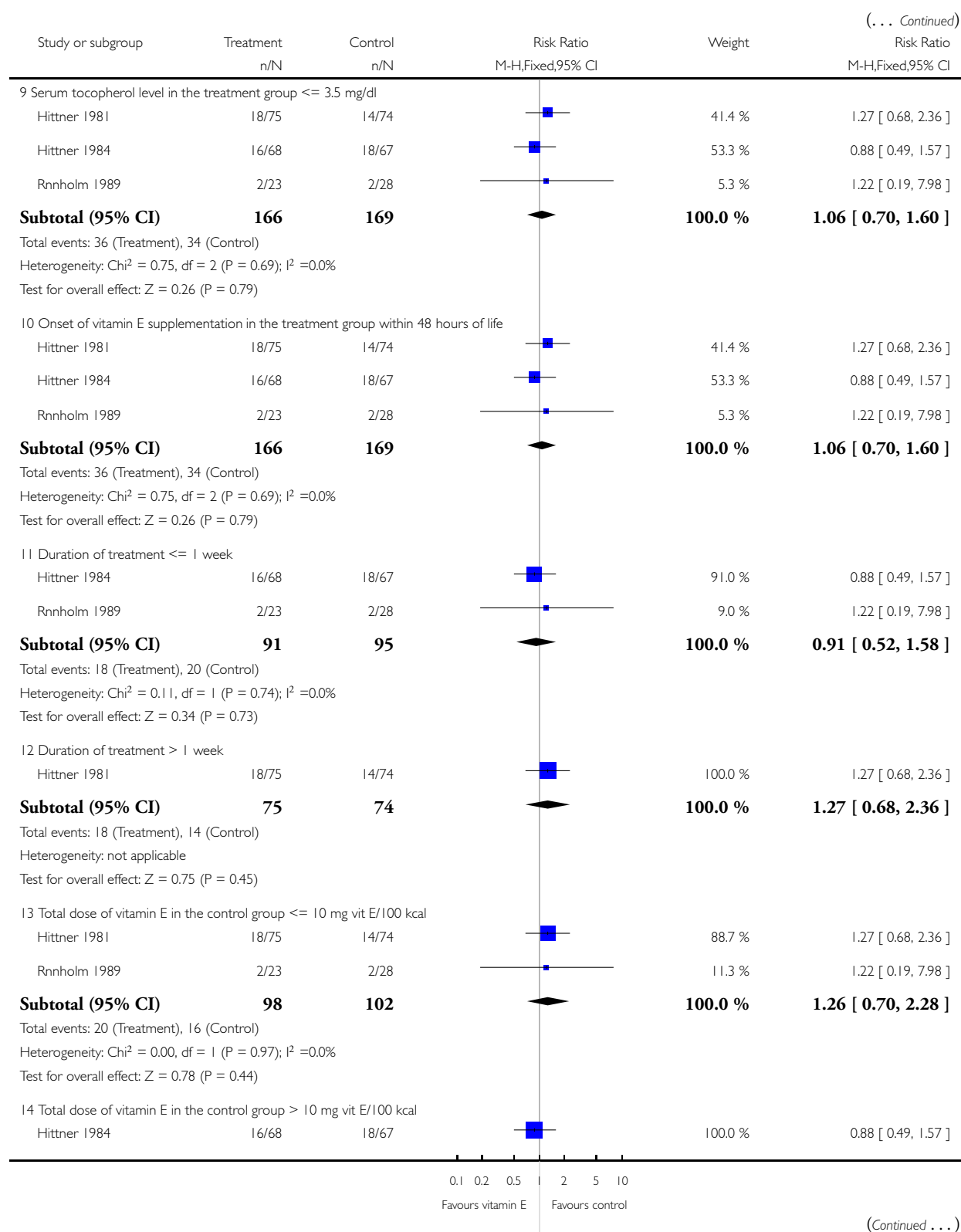
Comparison: 1 Vitamin E versus placebo or no vitamin E

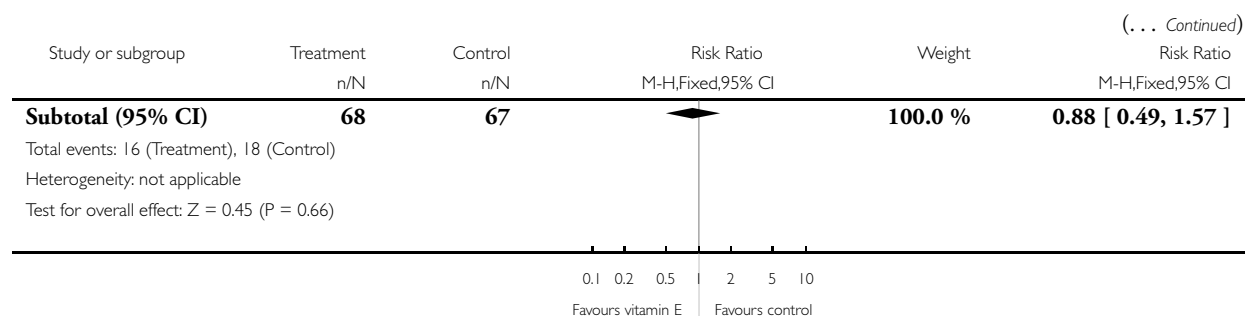
Outcome: 22 Germinal matrix/intraventricular hemorrhage among survivors



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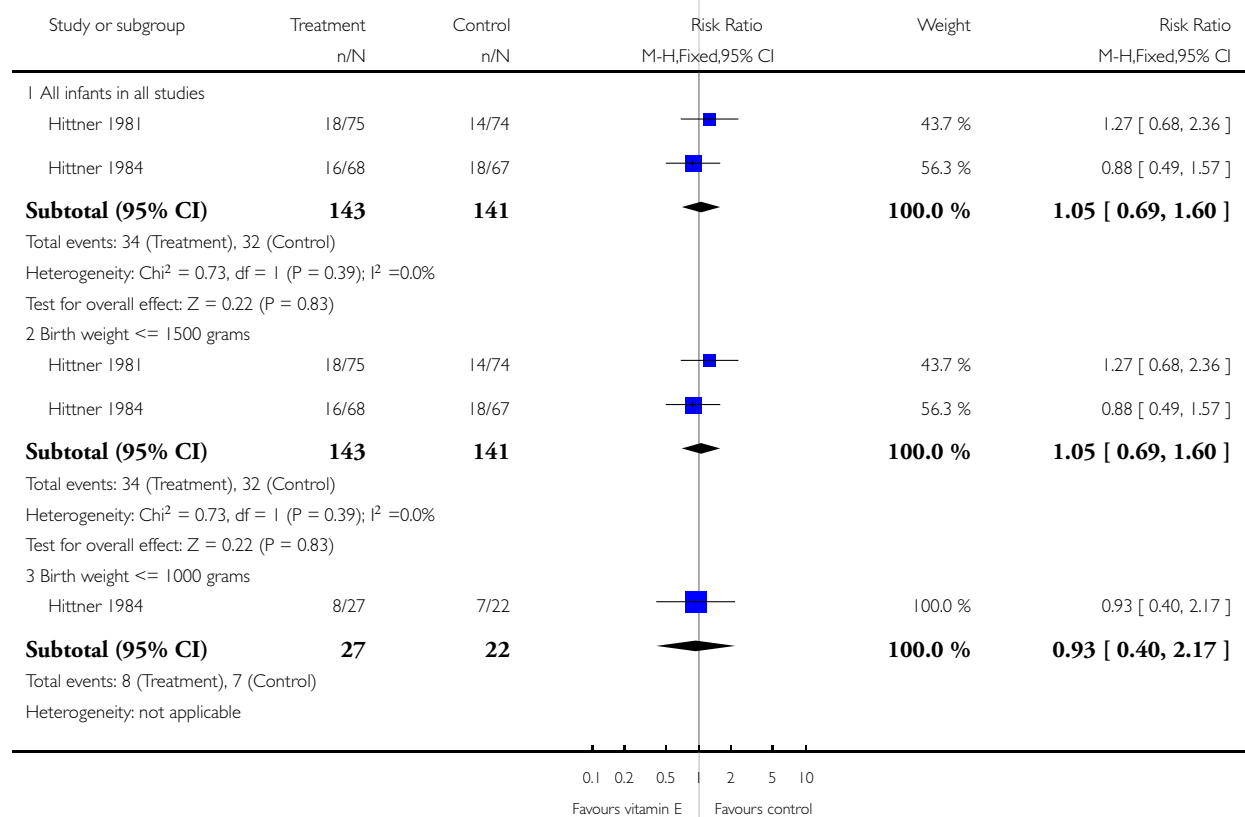


**Analysis 1.23. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 23 Germinal matrix/intraventricular hemorrhage among surviving very low birth weight infants.**

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

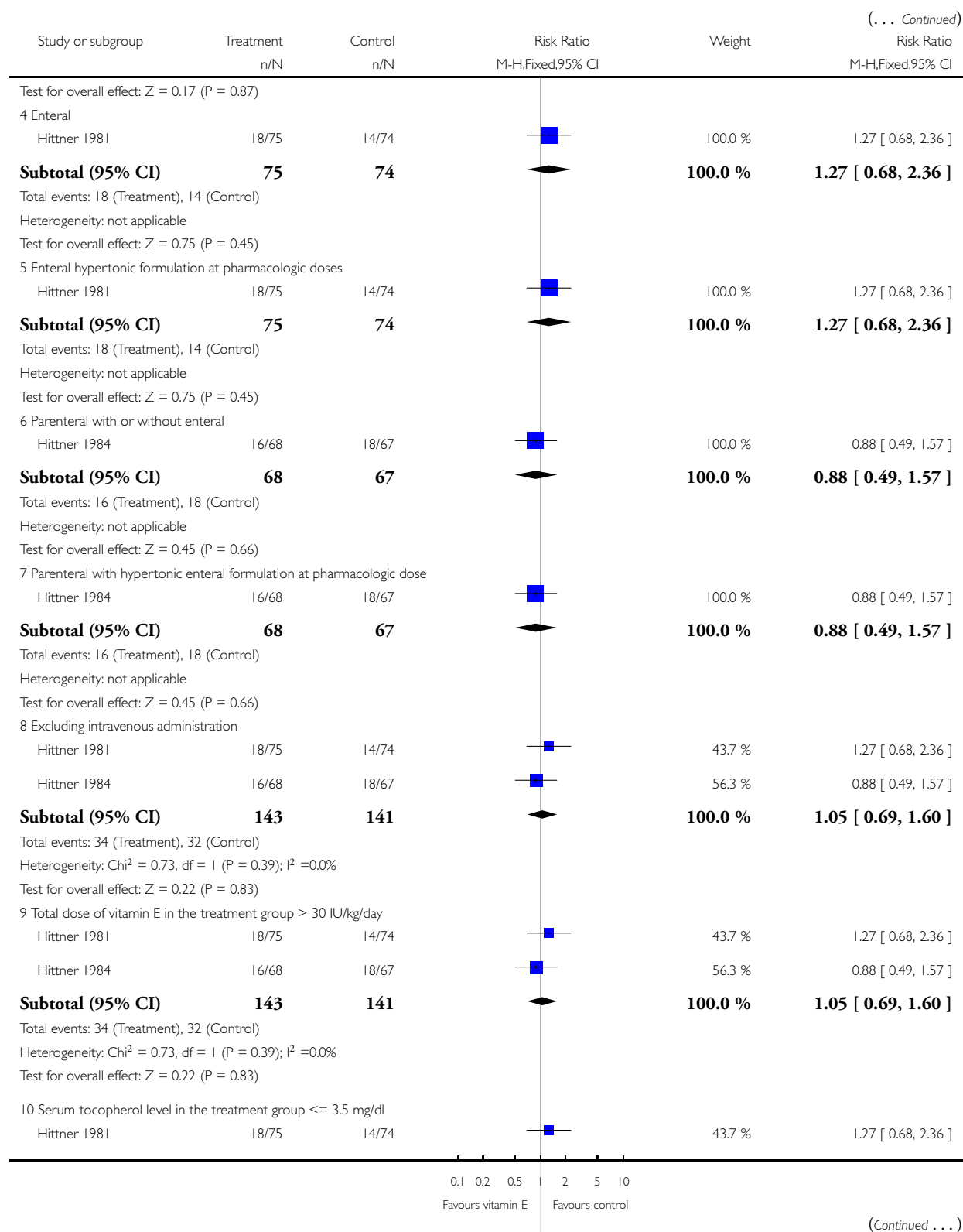
Comparison: 1 Vitamin E versus placebo or no vitamin E

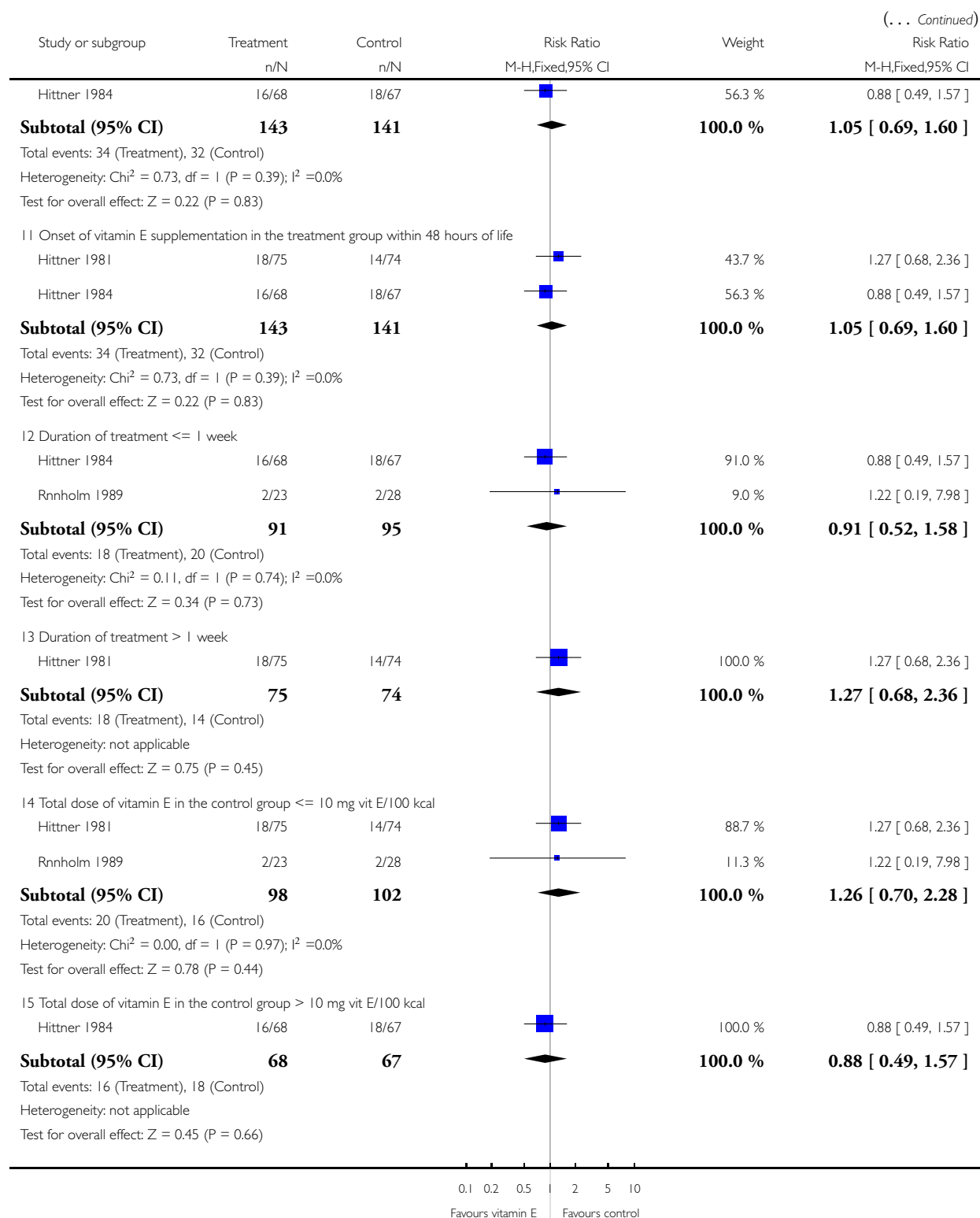
Outcome: 23 Germinal matrix/intraventricular hemorrhage among surviving very low birth weight infants



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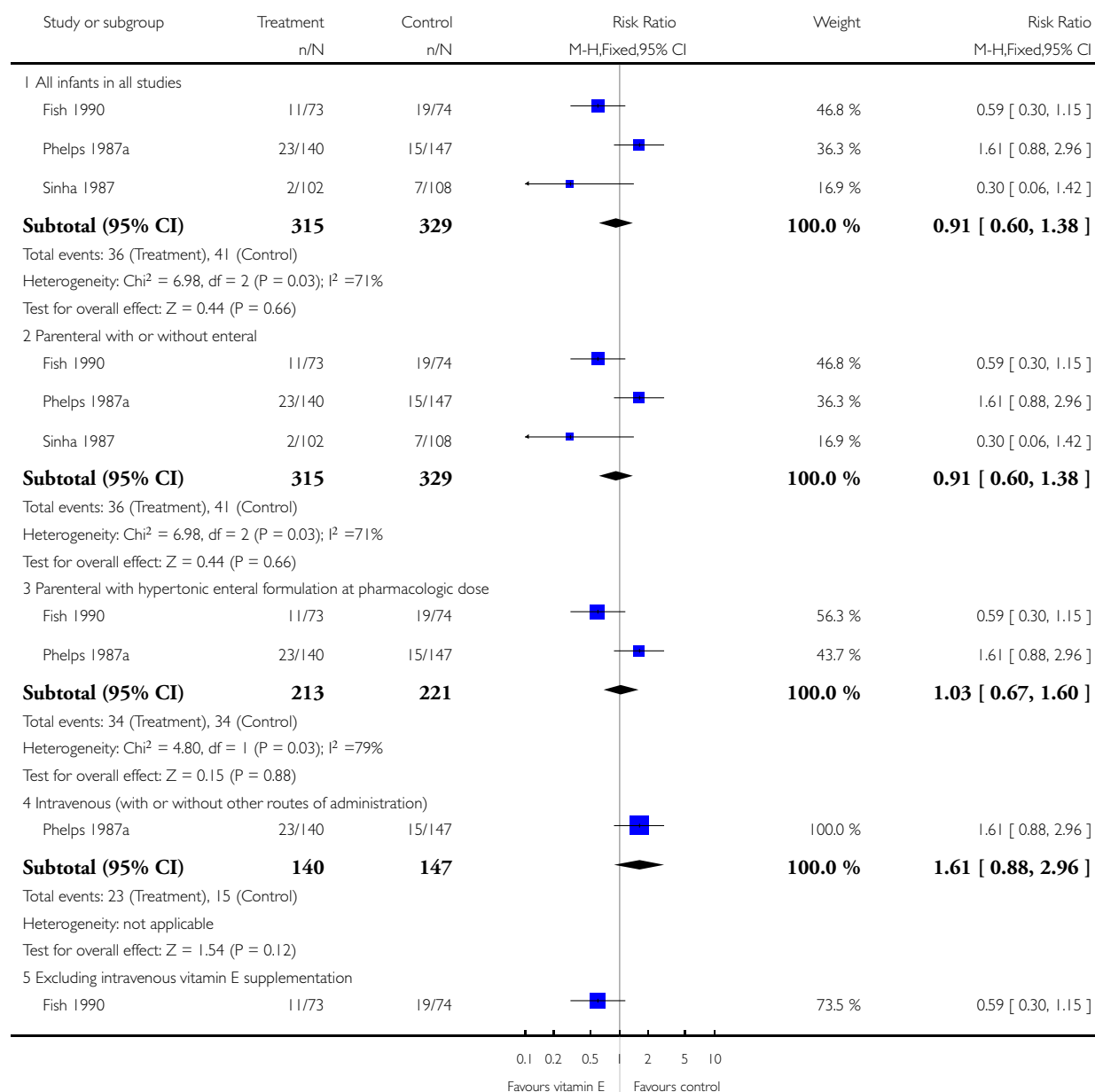


## Analysis 1.24. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 24 Severe intraventricular hemorrhage (grade III-IV).

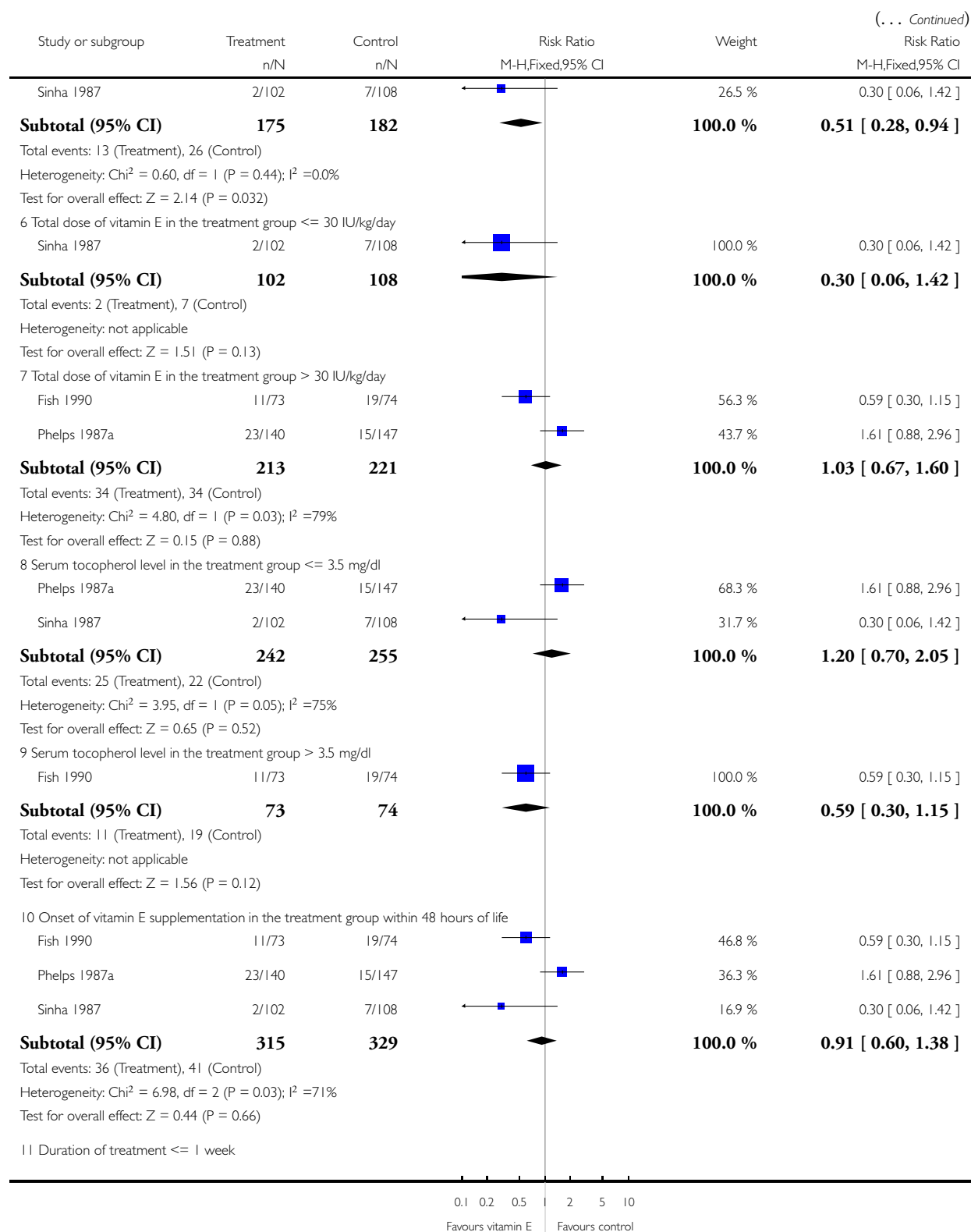
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

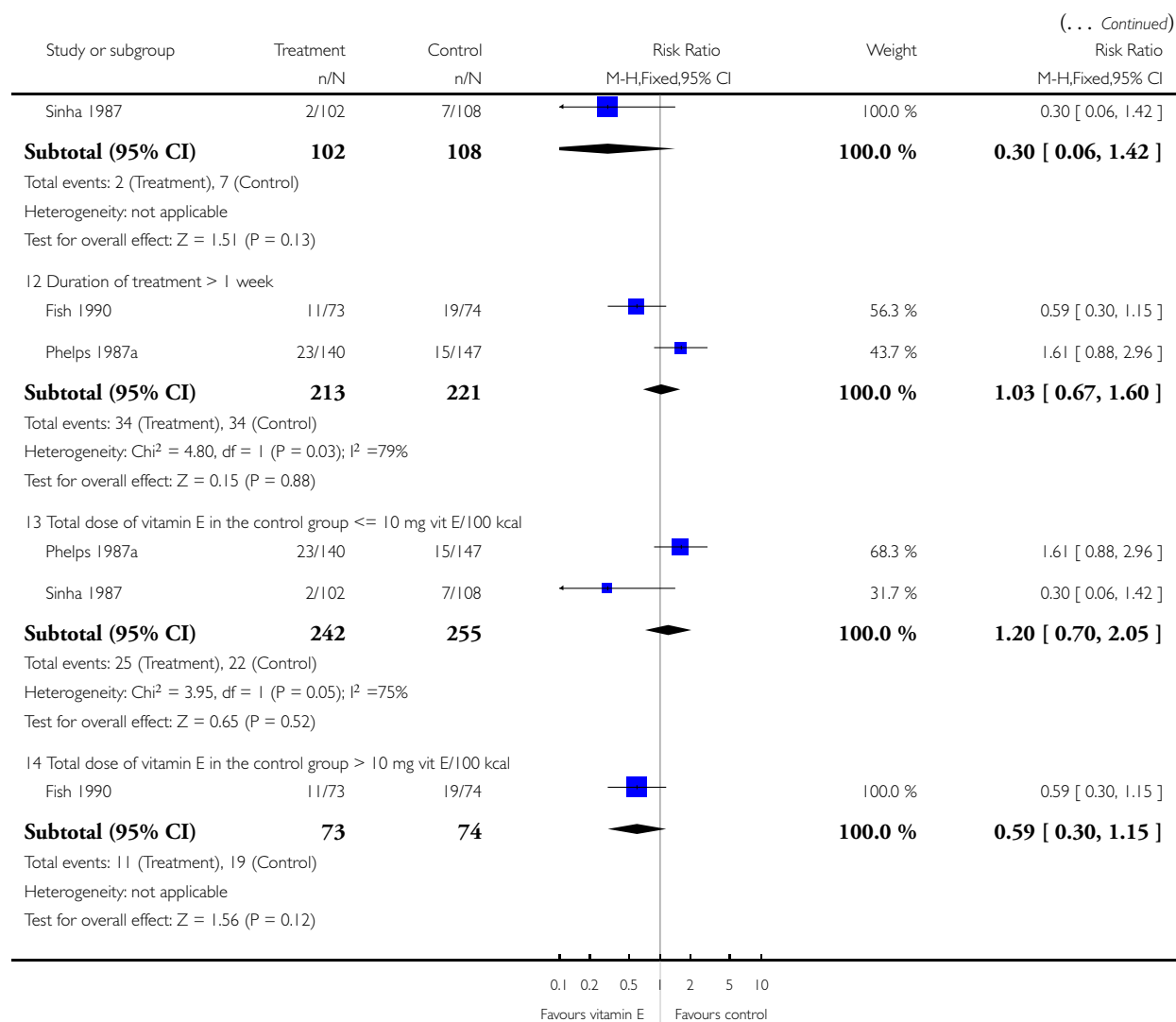
Outcome: 24 Severe intraventricular hemorrhage (grade III-IV)



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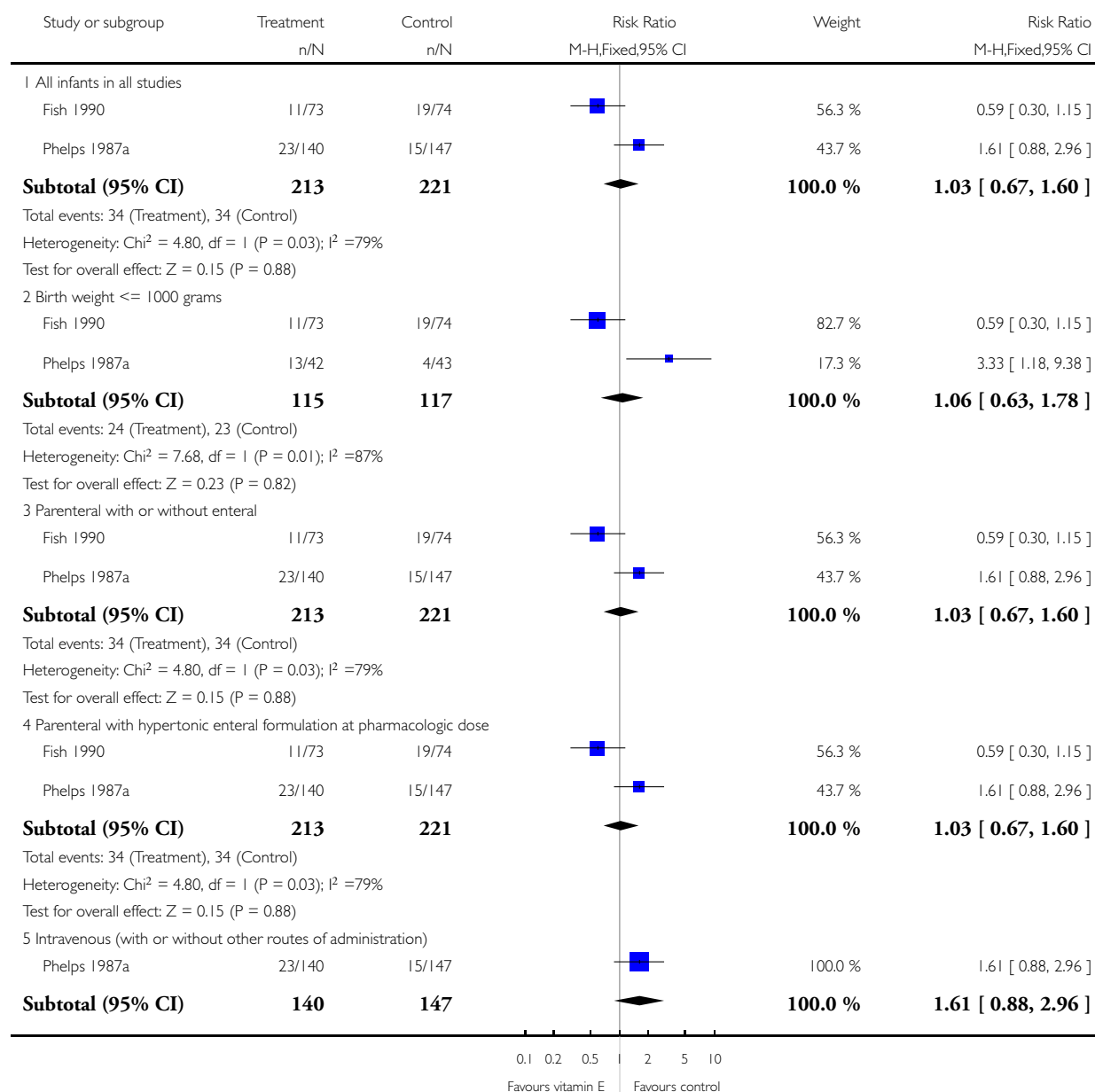


## Analysis 1.25. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 25 Severe intraventricular hemorrhage among very low birth weight infants.

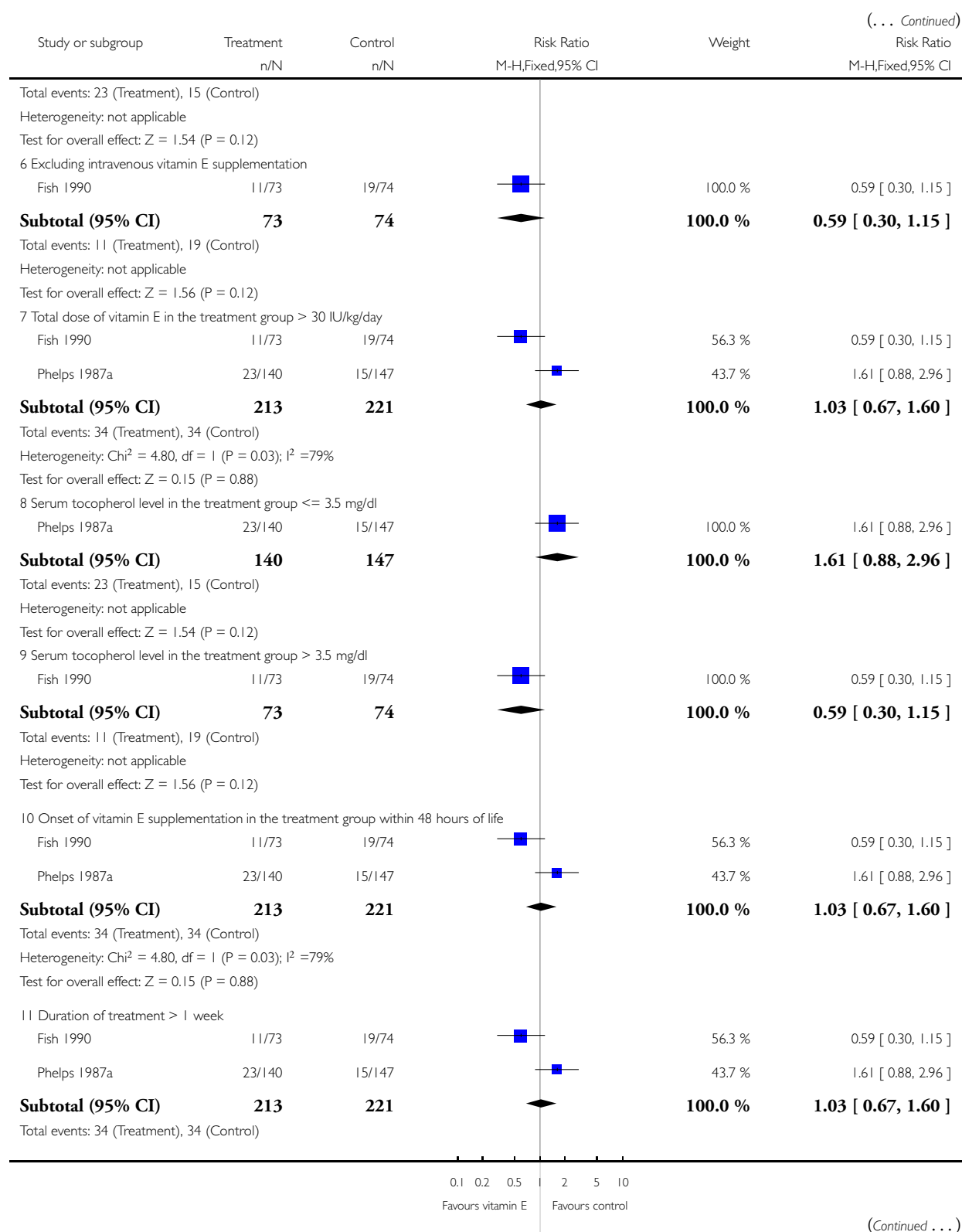
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

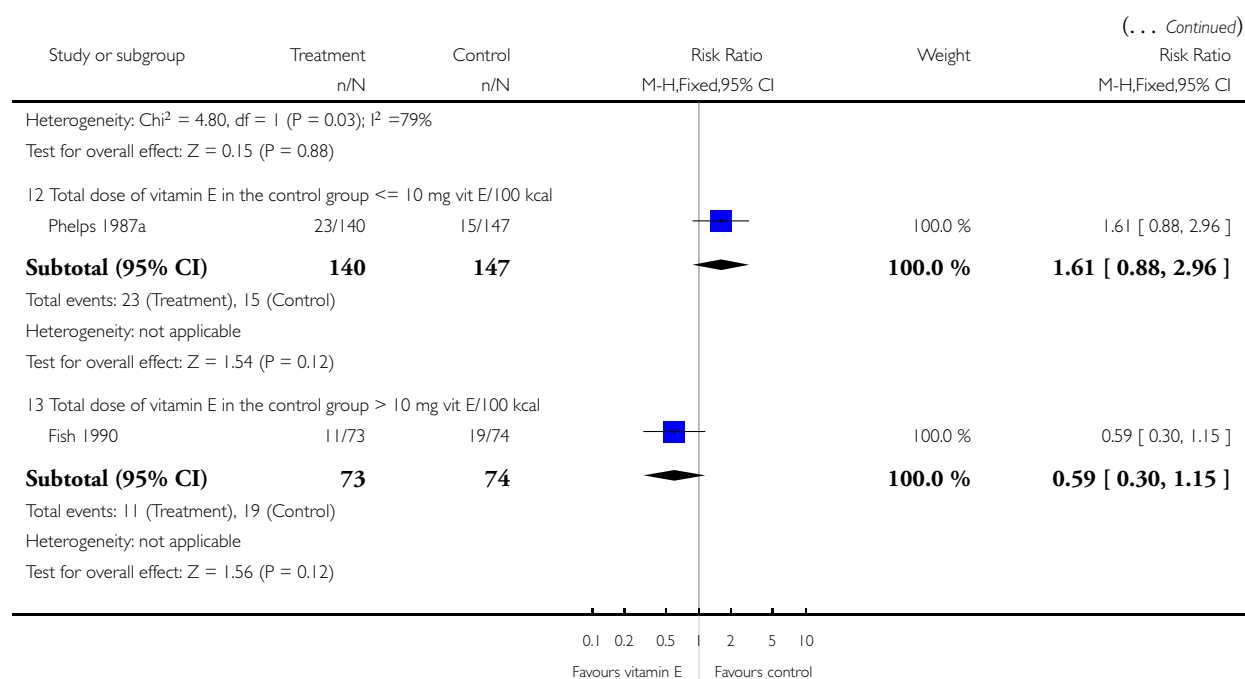
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 25 Severe intraventricular hemorrhage among very low birth weight infants



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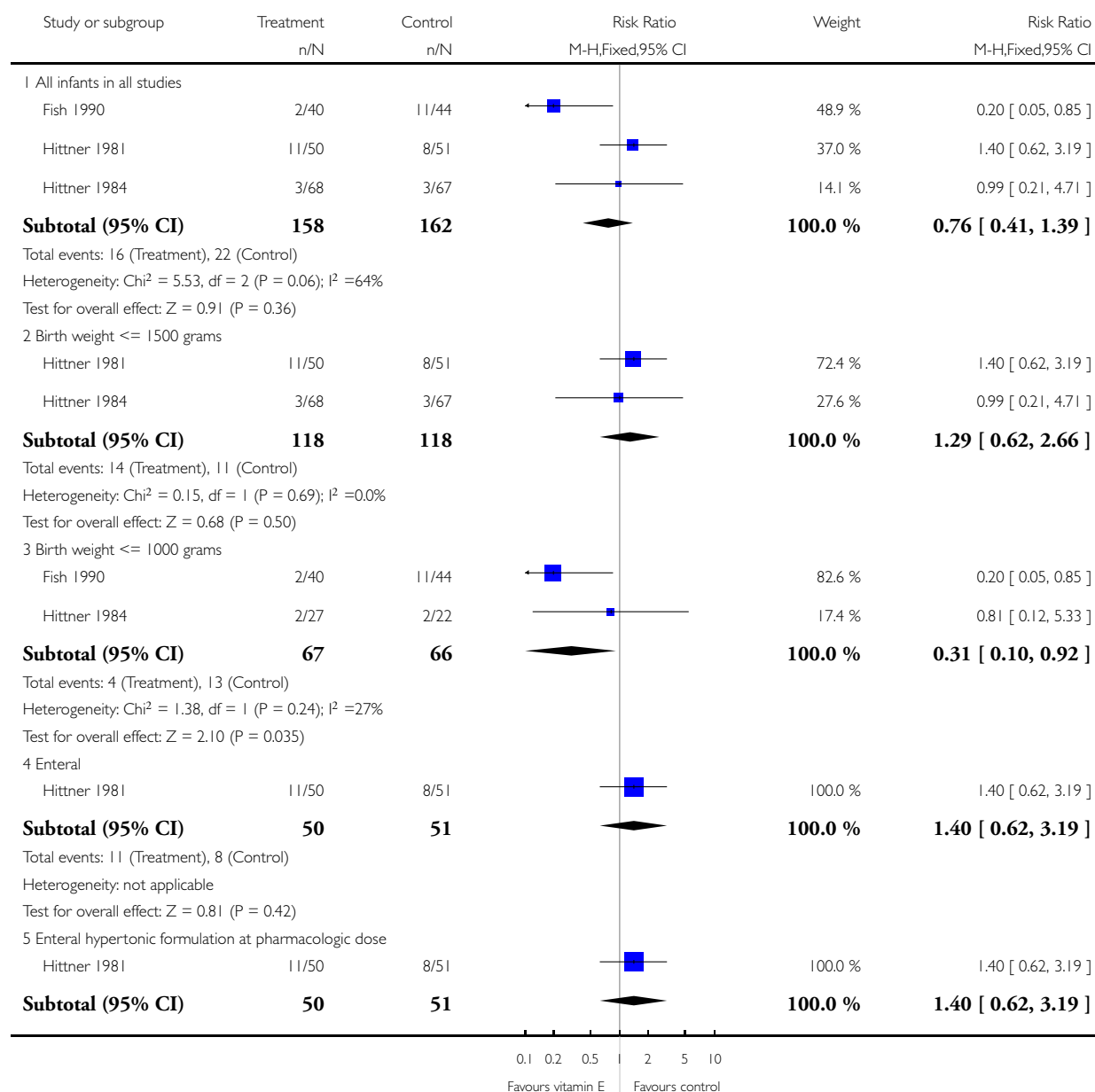


## Analysis 1.26. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 26 Severe intraventricular hemorrhage among surviving very low birth weight infants.

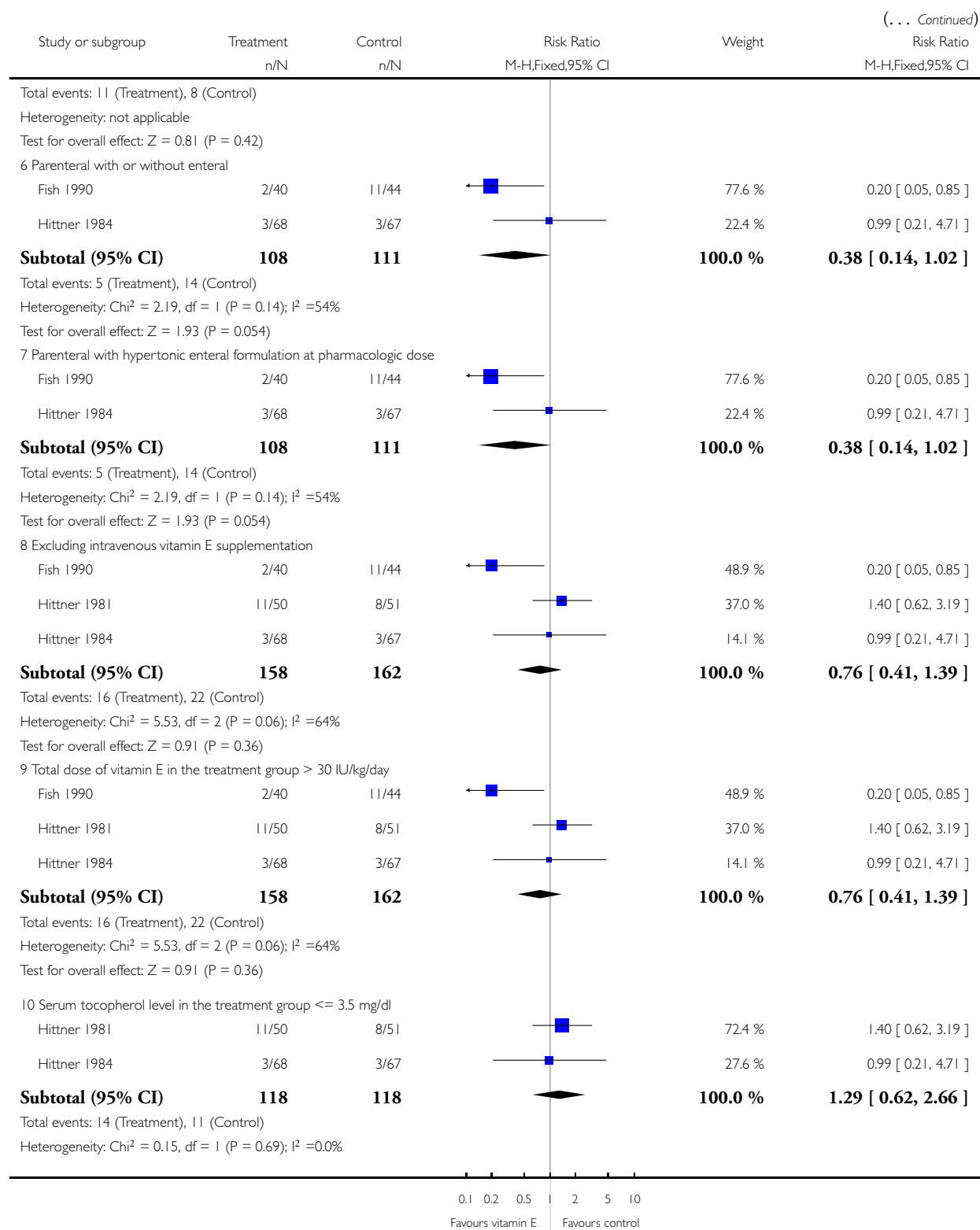
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

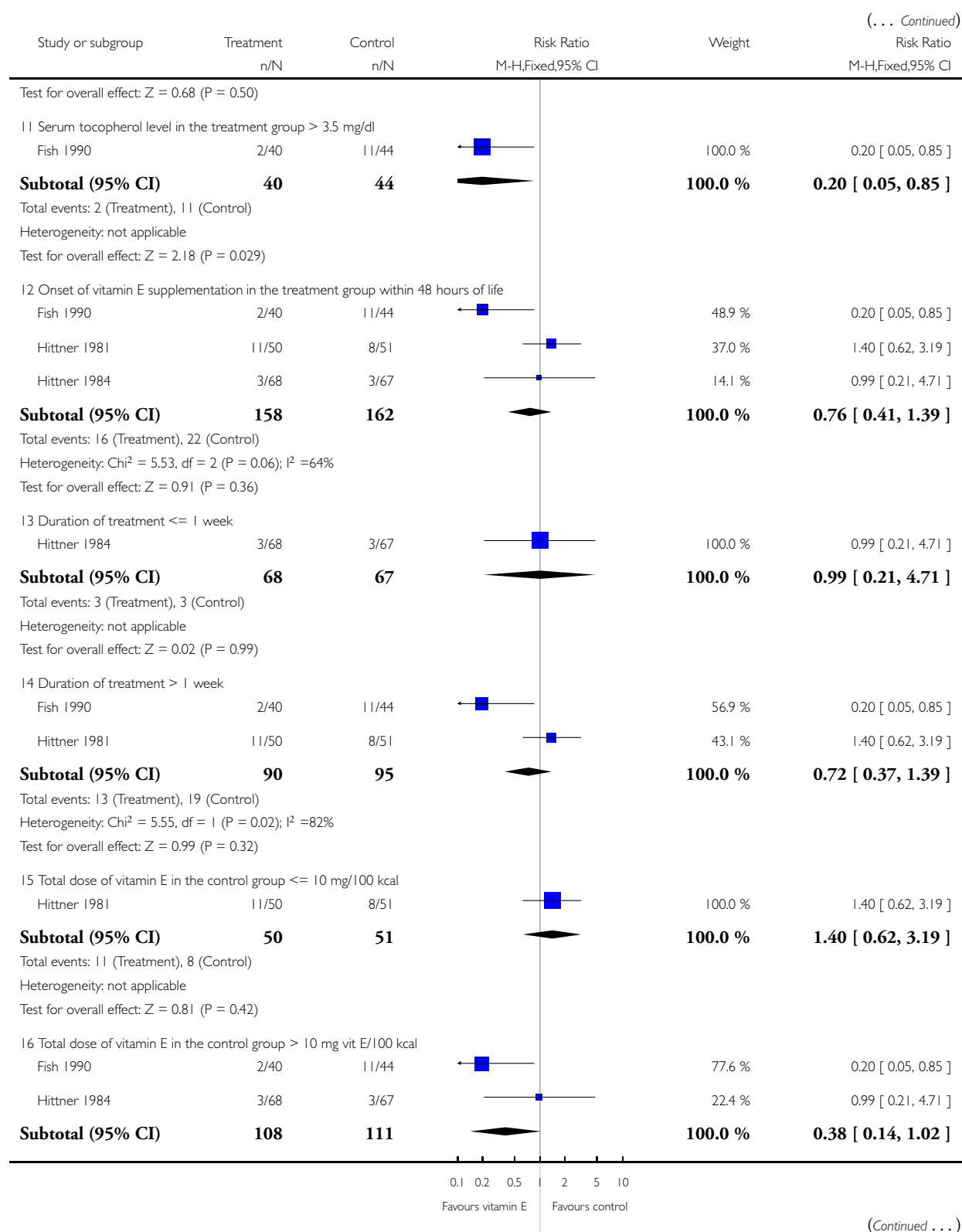
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 26 Severe intraventricular hemorrhage among surviving very low birth weight infants

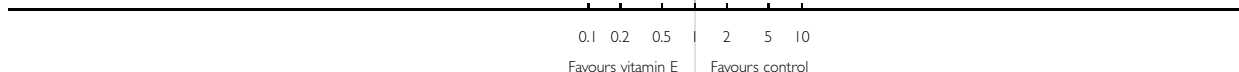


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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 5 (Treatment), 14 (Control)					
Heterogeneity: Chi² = 2.19, df = 1 (P = 0.14); I² = 54%					
Test for overall effect: Z = 1.93 (P = 0.054)					

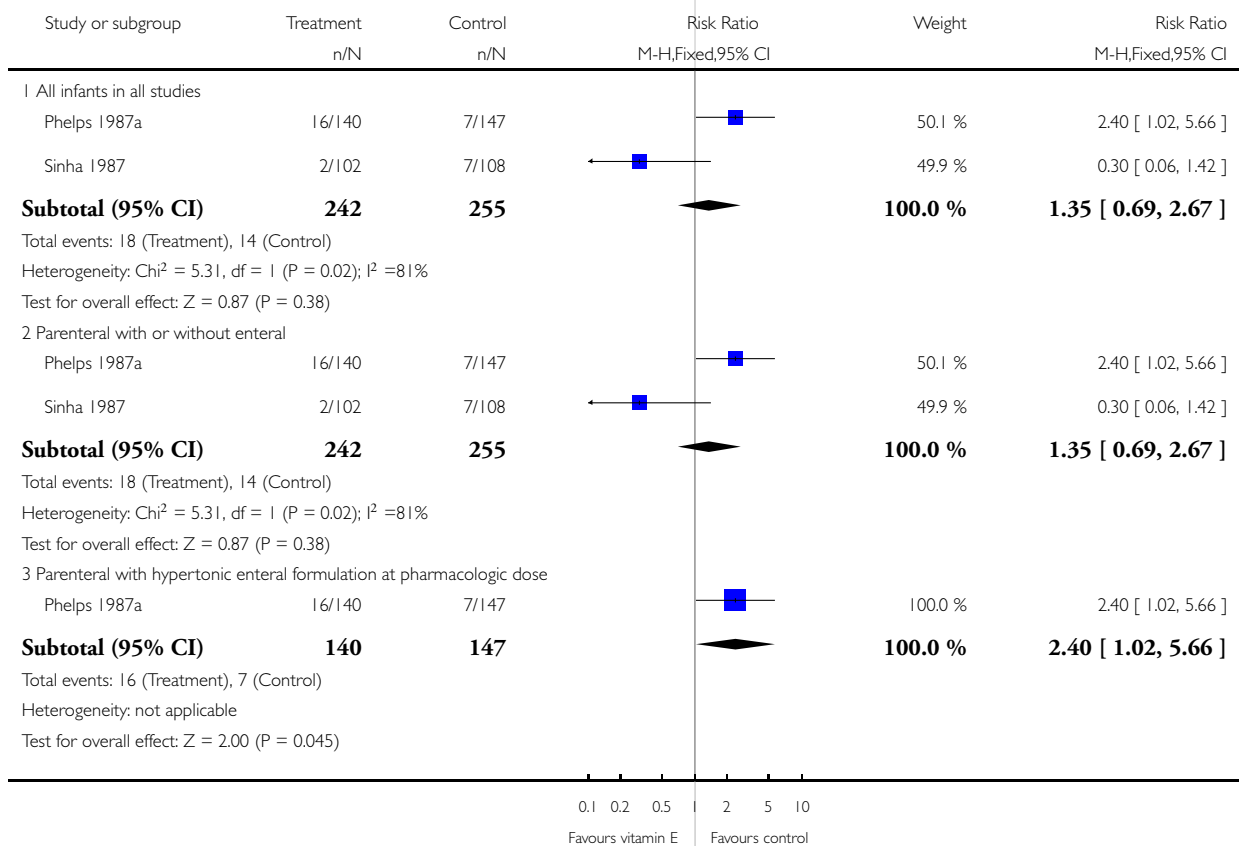


### Analysis 1.27. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 27 Parenchymal hemorrhage (grade IV).

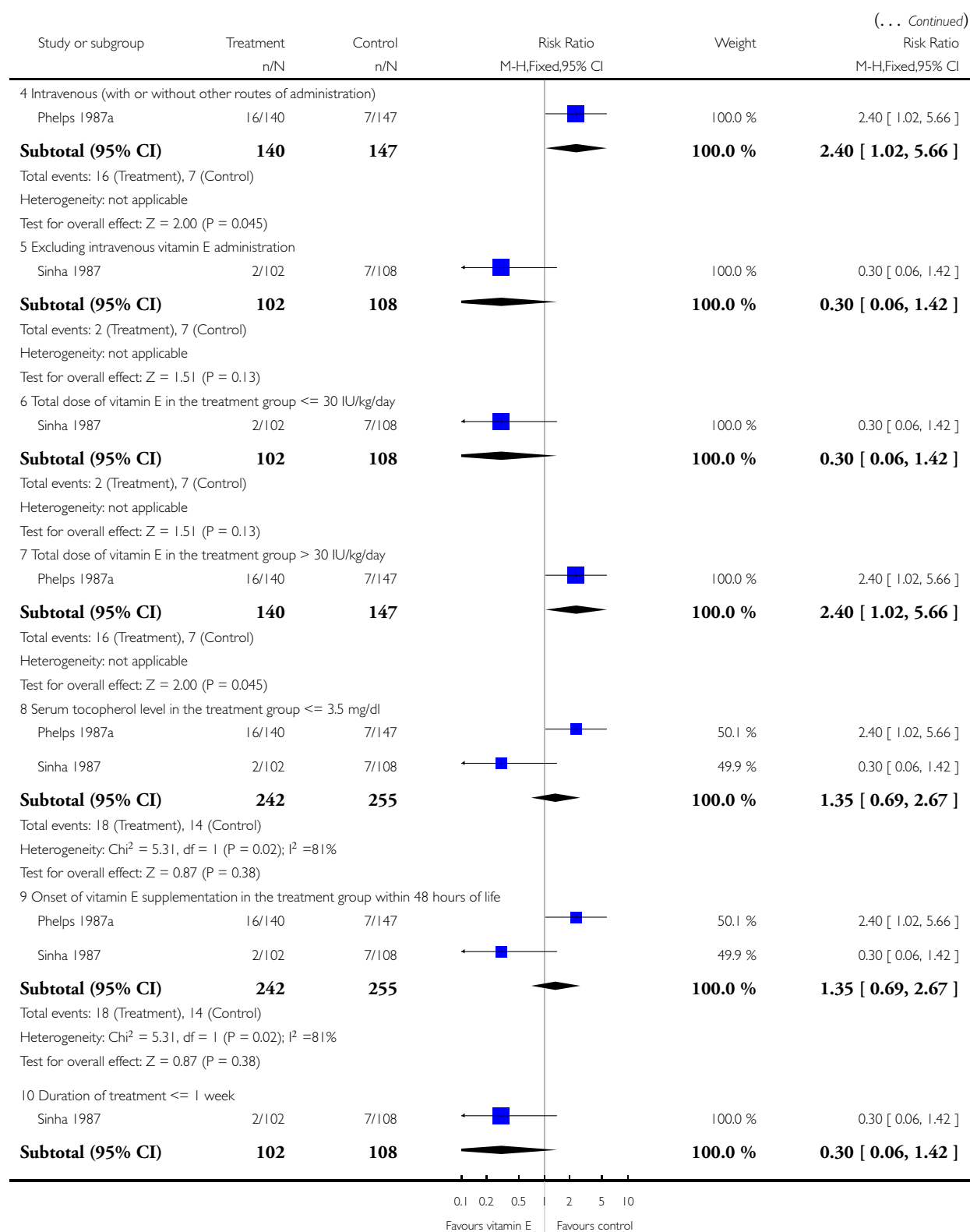
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

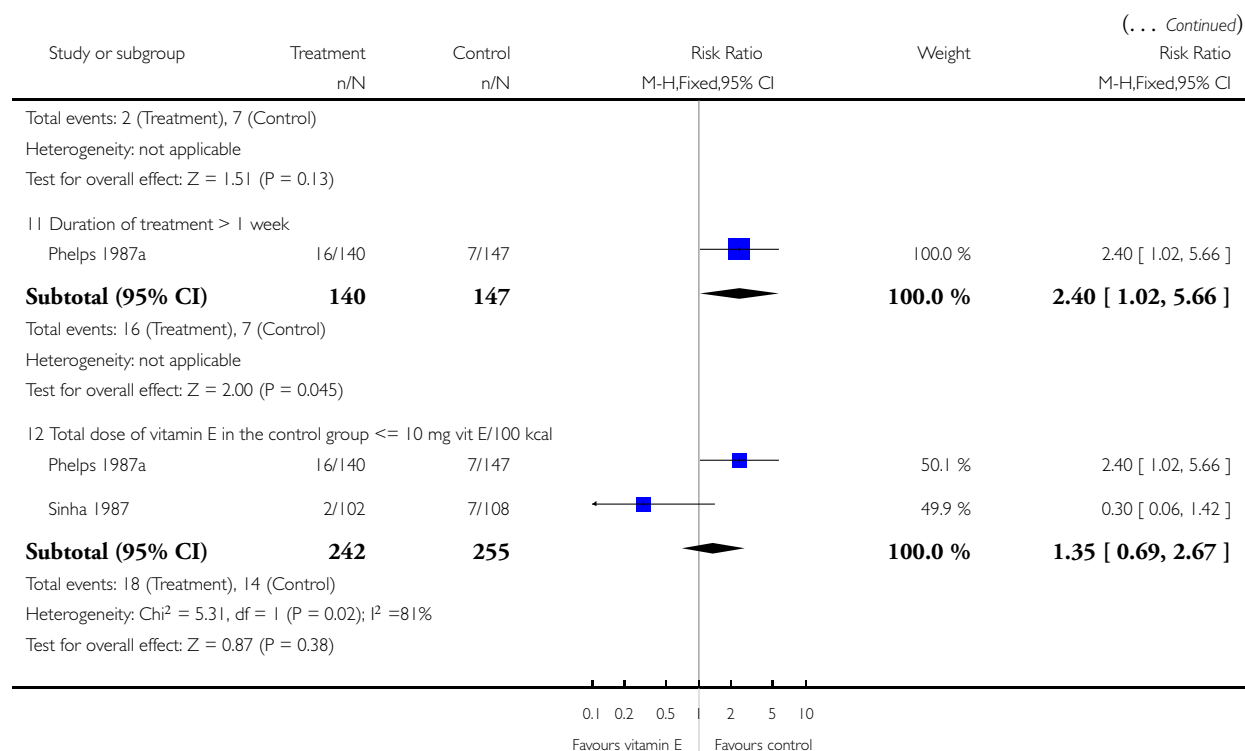
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 27 Parenchymal hemorrhage (grade IV)



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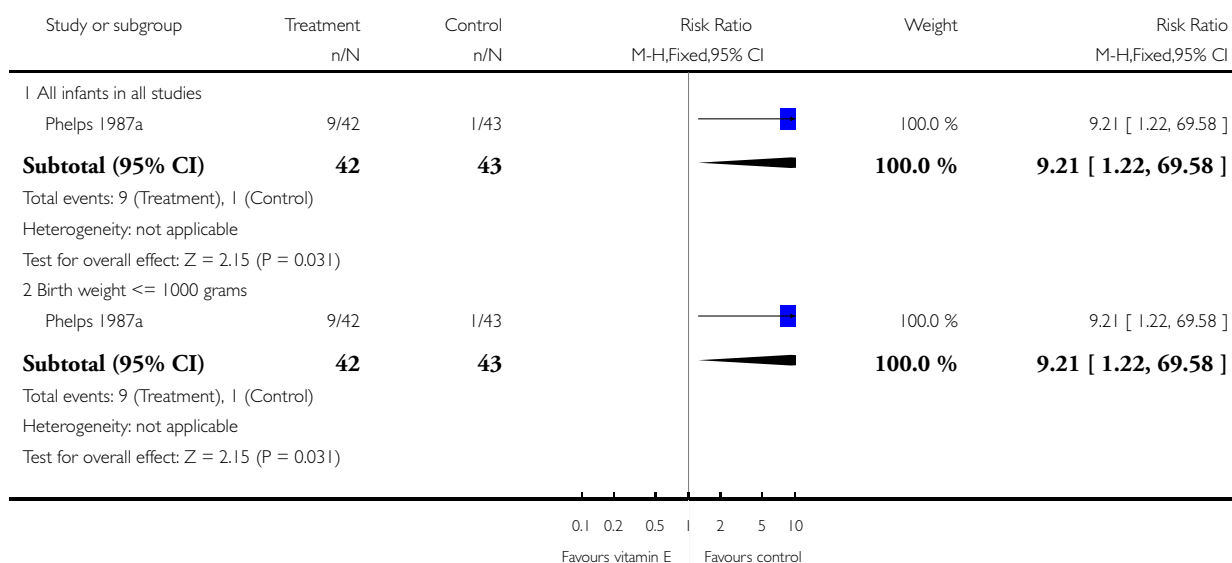


### Analysis 1.28. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 28 Parenchymal hemorrhage among very low birth weight infants.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 28 Parenchymal hemorrhage among very low birth weight infants

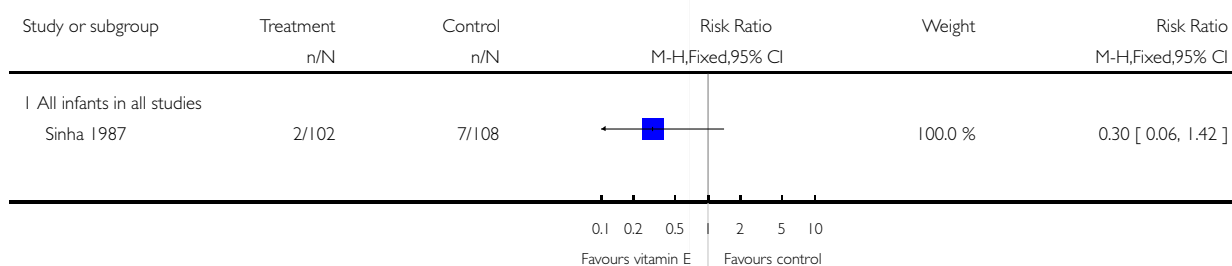


### Analysis 1.29. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 29 Parenchymal hemorrhage among patients with negative initial ultrasonogram.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 29 Parenchymal hemorrhage among patients with negative initial ultrasonogram

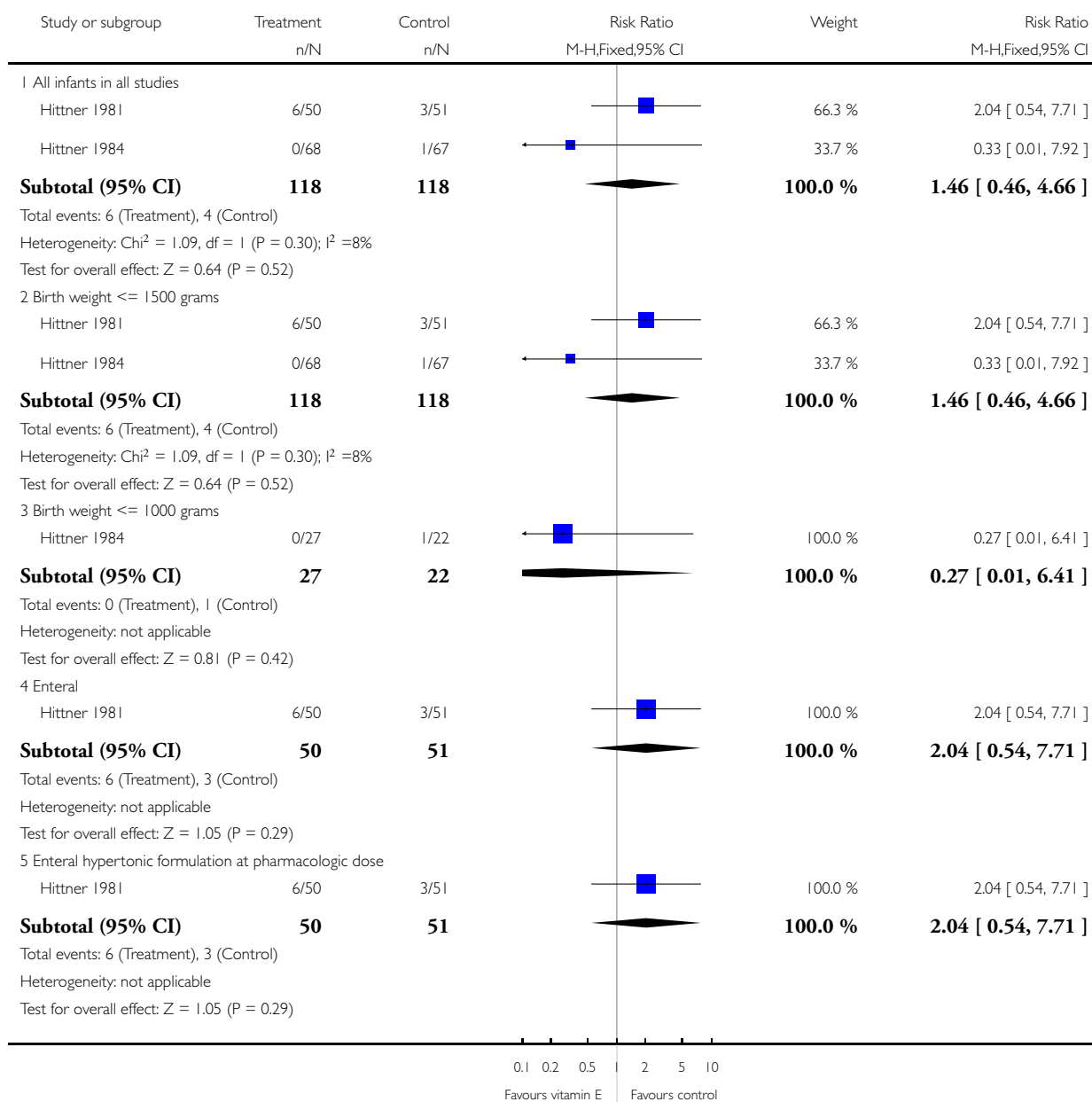


### Analysis 1.30. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 30 Parenchymal hemorrhage (Grade IV) among surviving very low birth weight infants.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

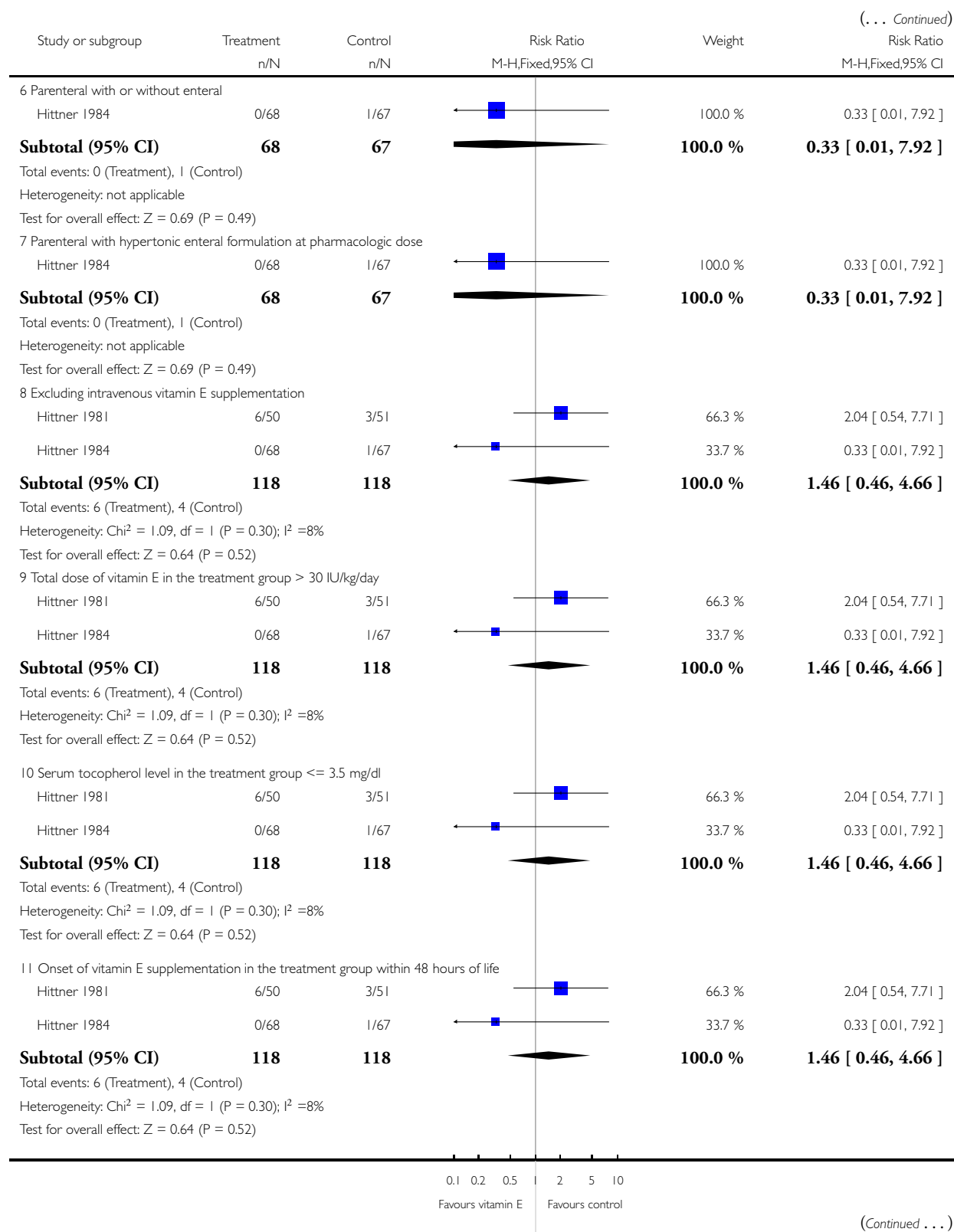
Comparison: 1 Vitamin E versus placebo or no vitamin E

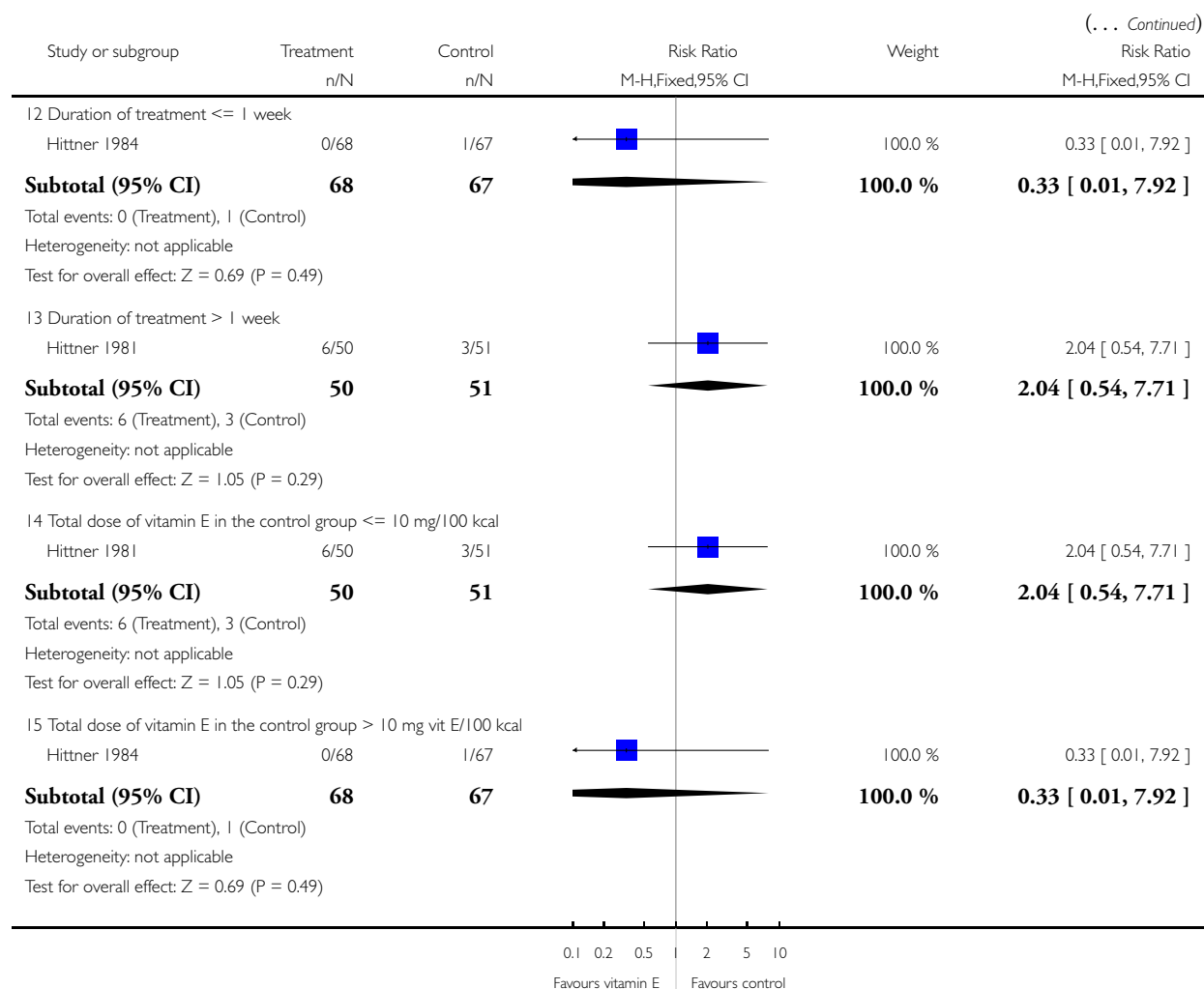
Outcome: 30 Parenchymal hemorrhage (Grade IV) among surviving very low birth weight infants



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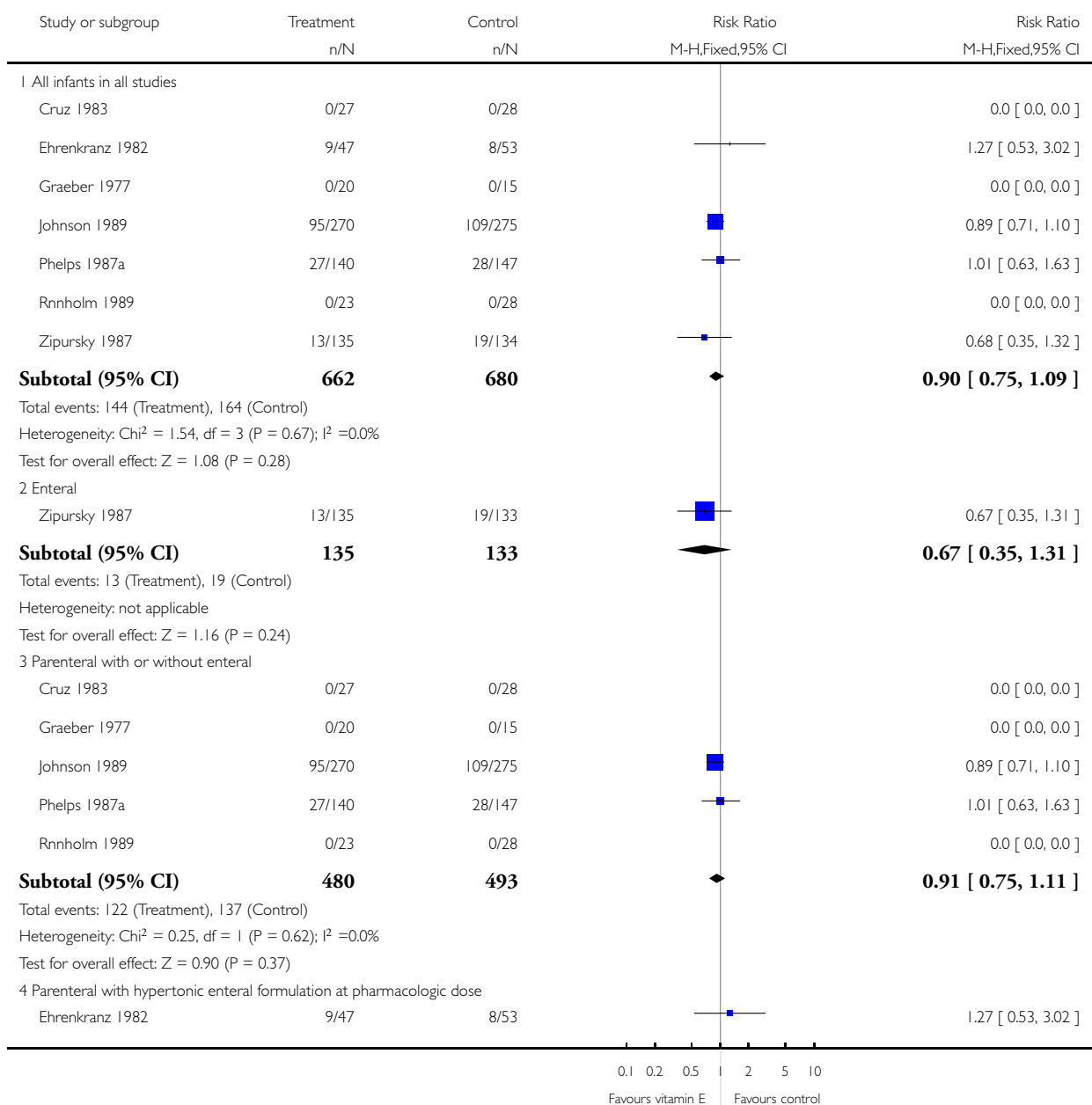


### Analysis 1.31. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 31 Retrolental fibroplasia/retinopathy of prematurity.

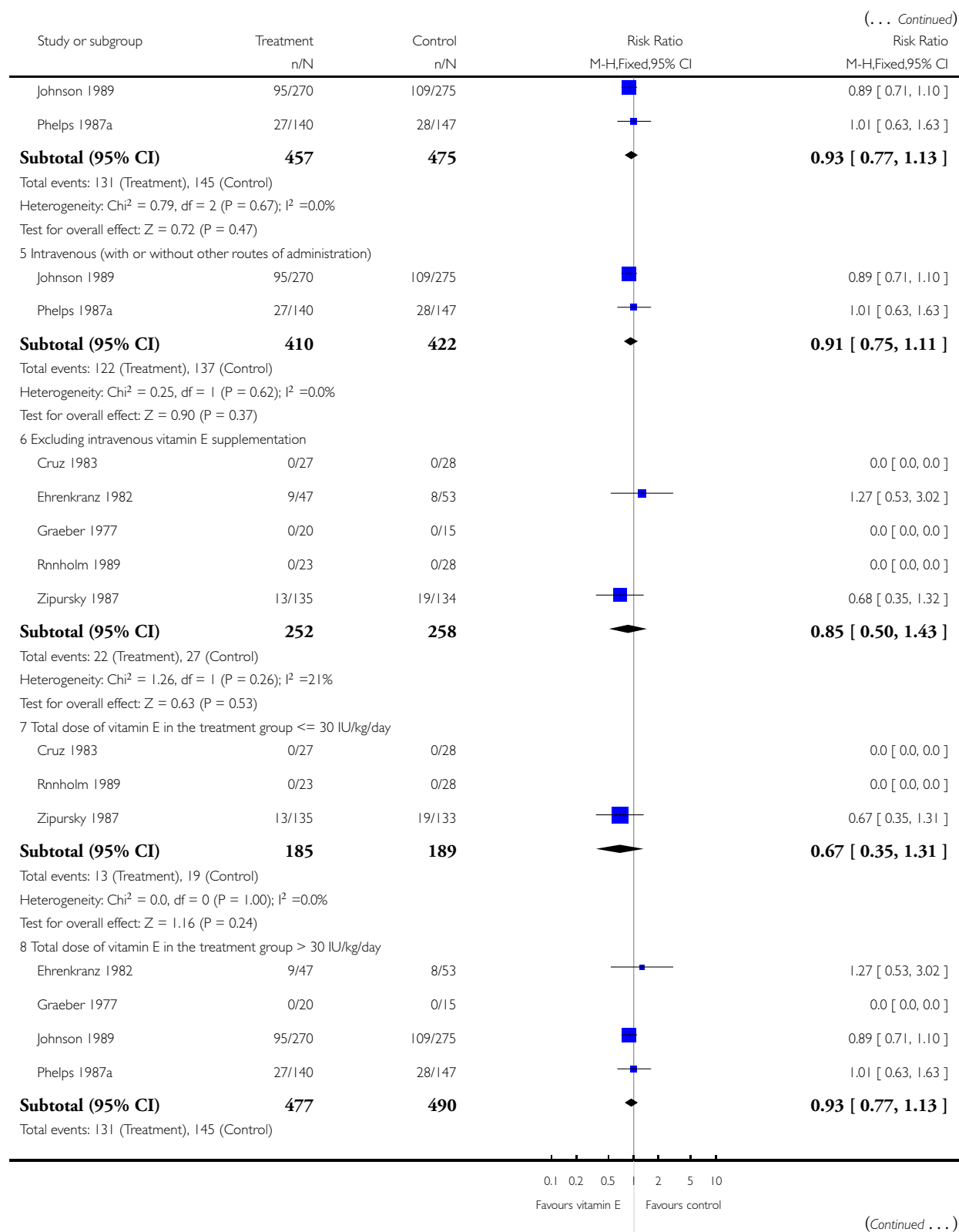
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

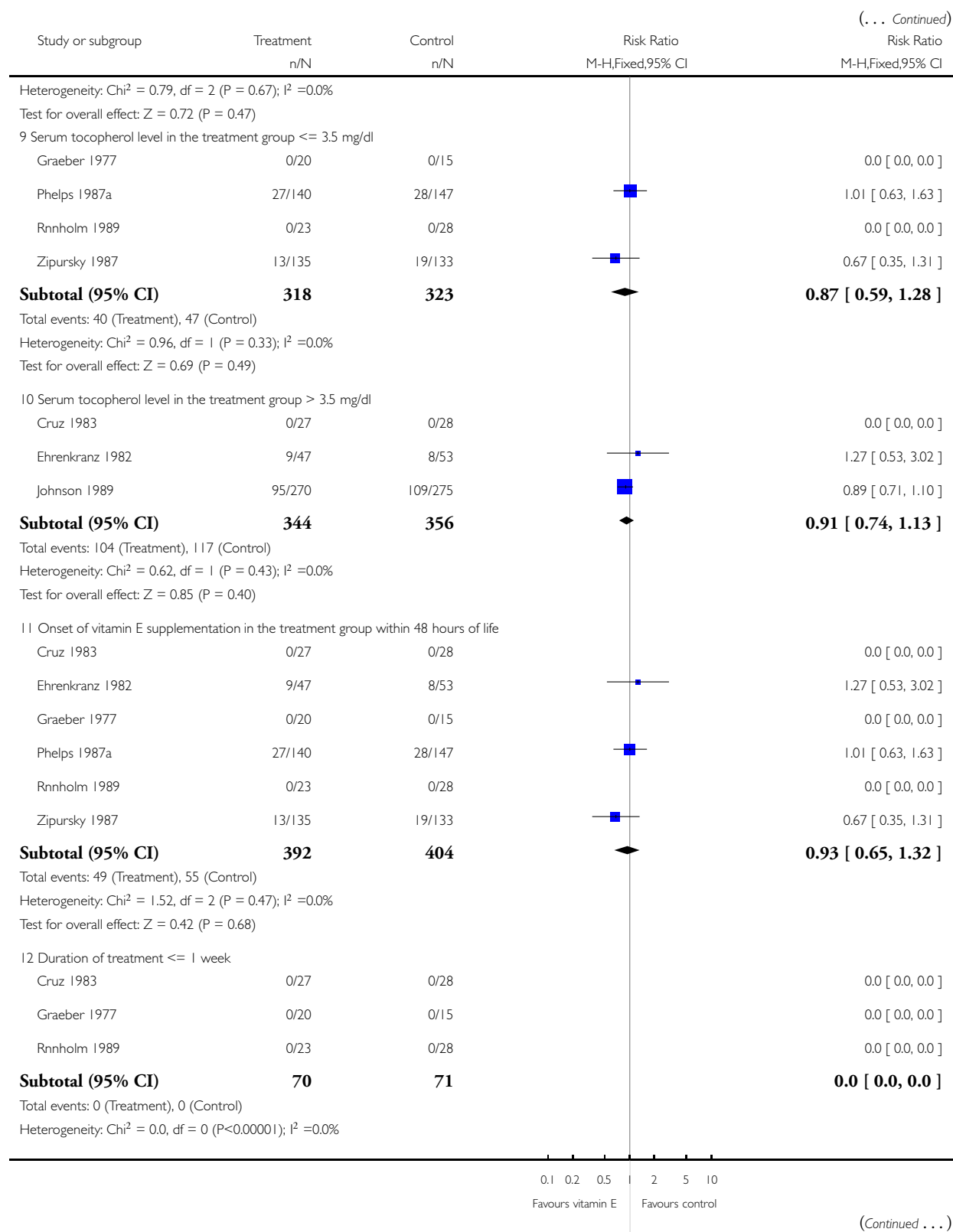
Comparison: 1 Vitamin E versus placebo or no vitamin E

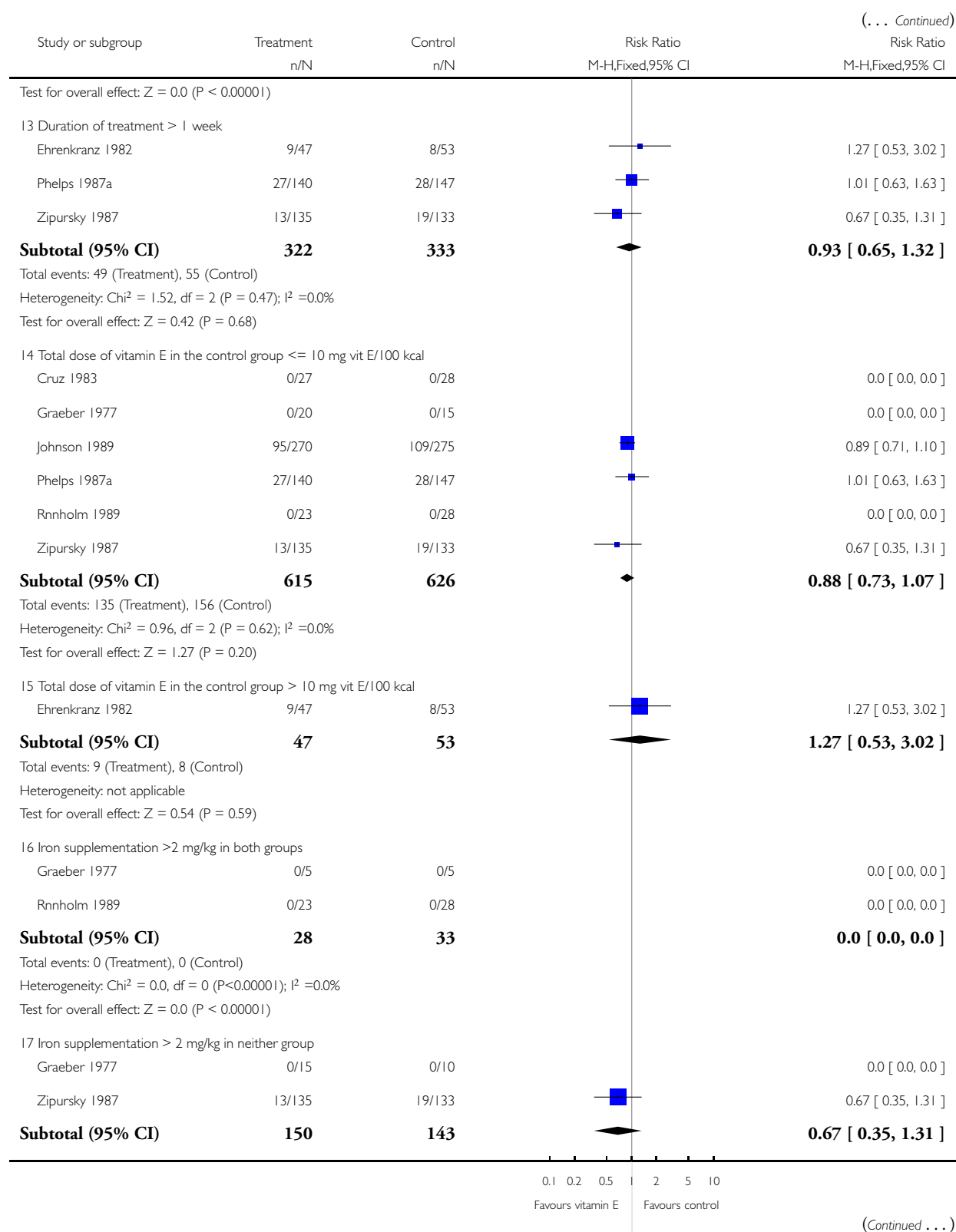
Outcome: 31 Retrolental fibroplasia/retinopathy of prematurity

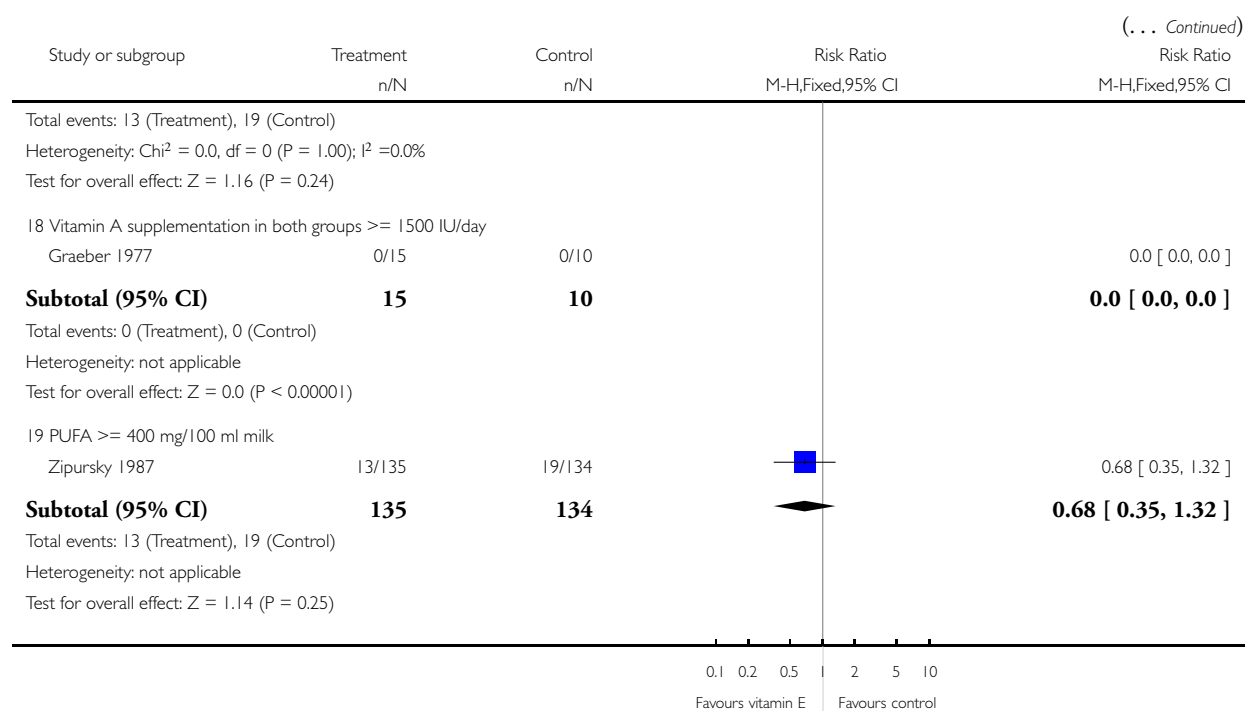


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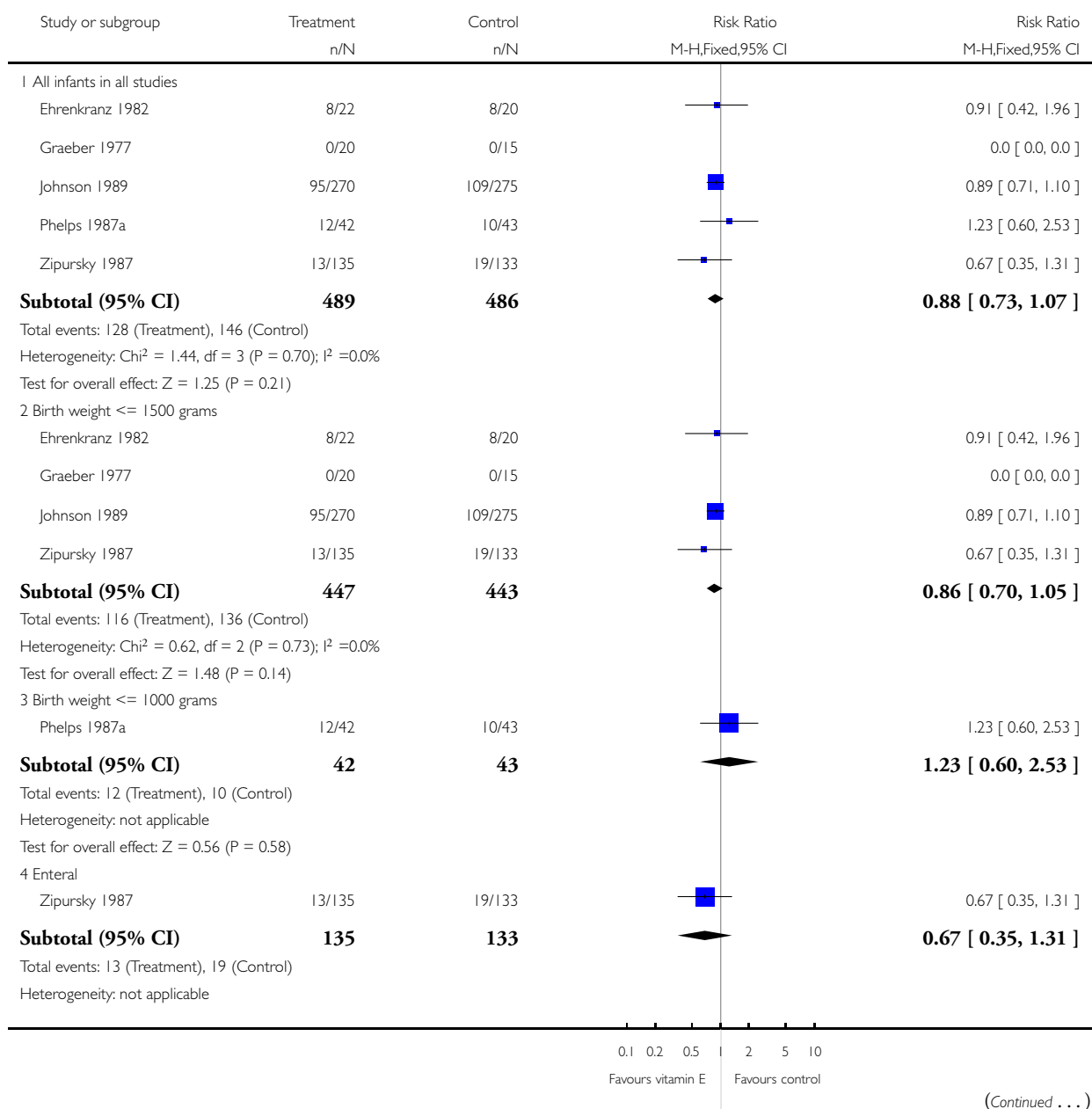


### Analysis 1.32. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 32 Retrolental fibroplasia/retinopathy of prematurity among very low birth weight infants.

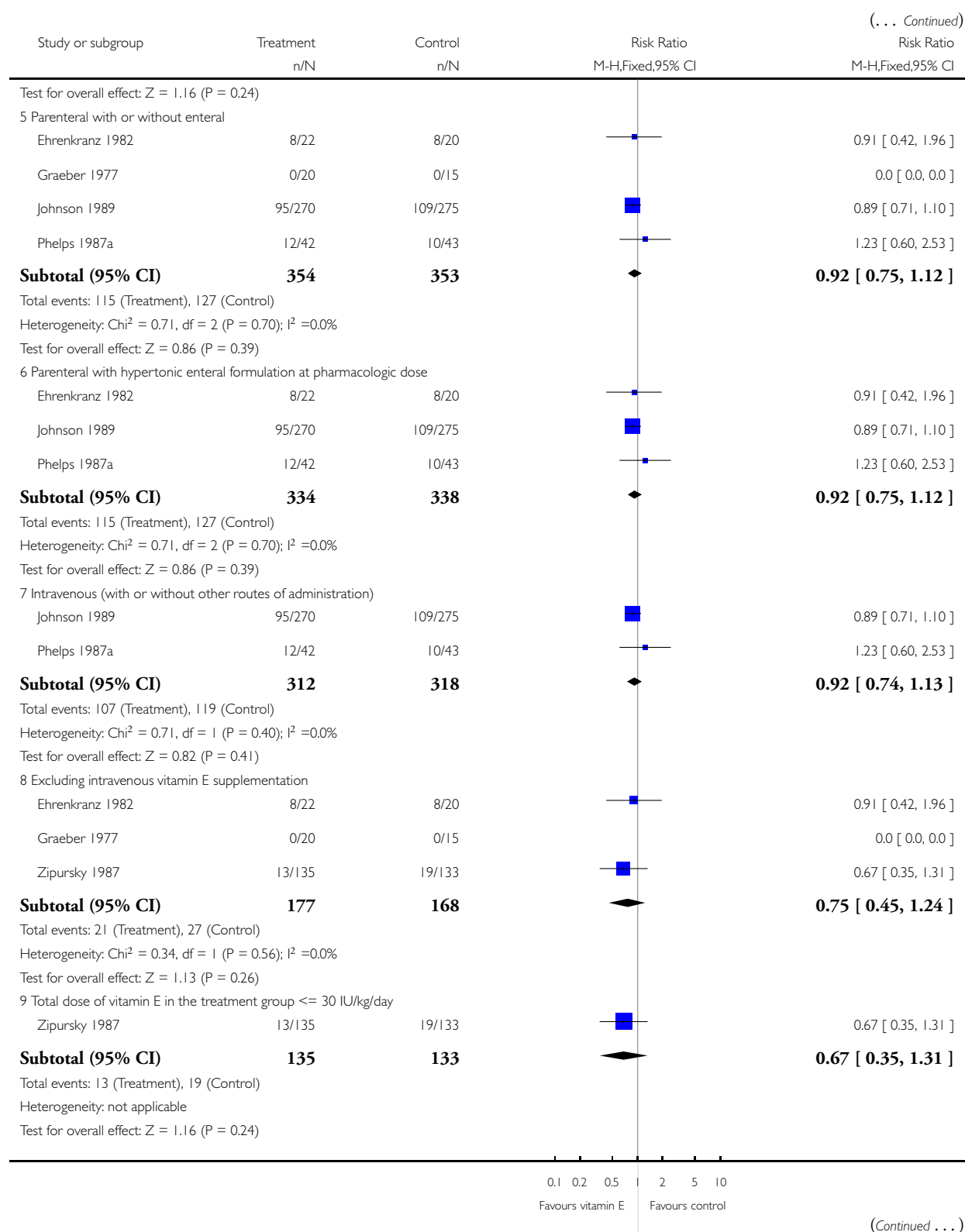
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

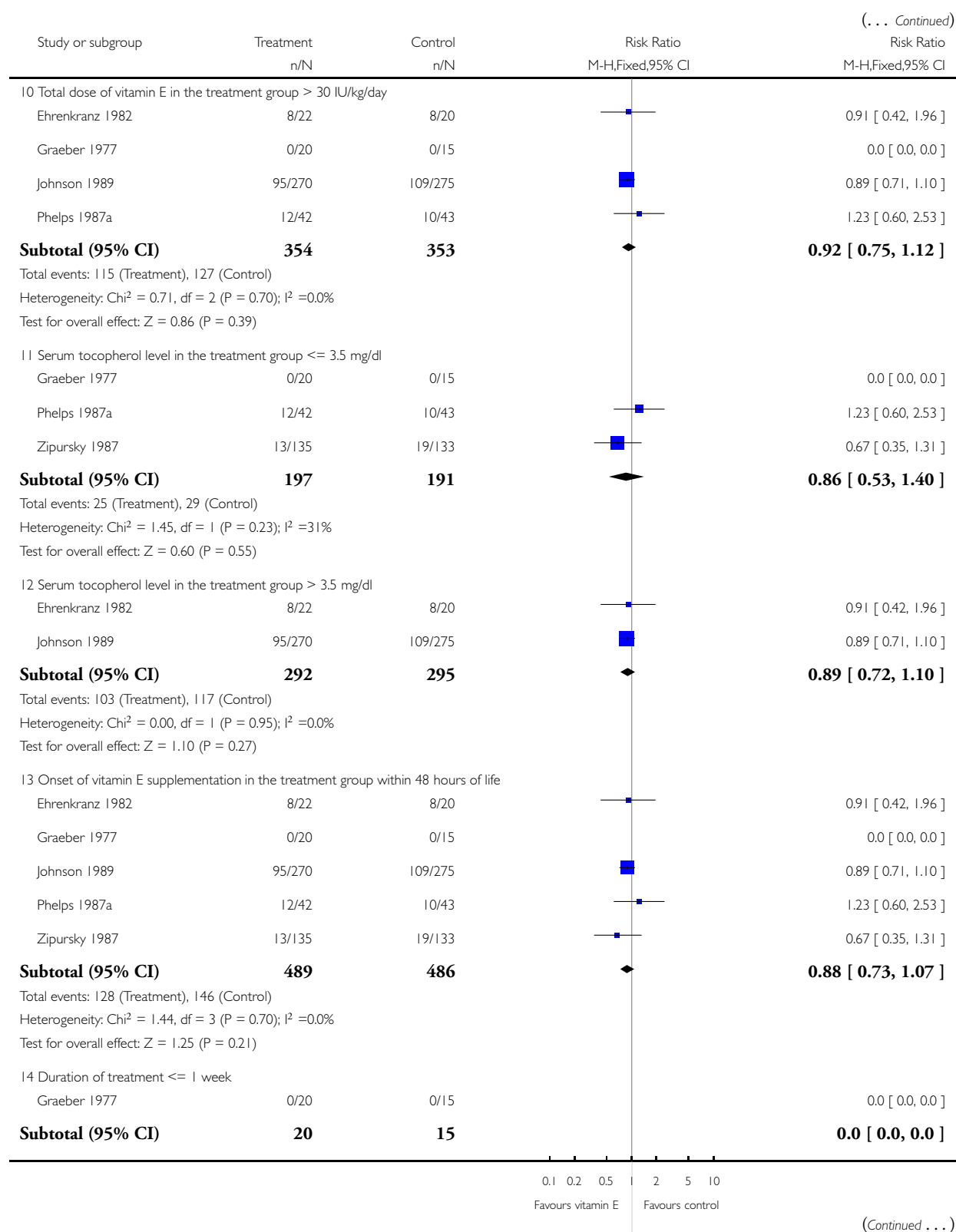
Comparison: 1 Vitamin E versus placebo or no vitamin E

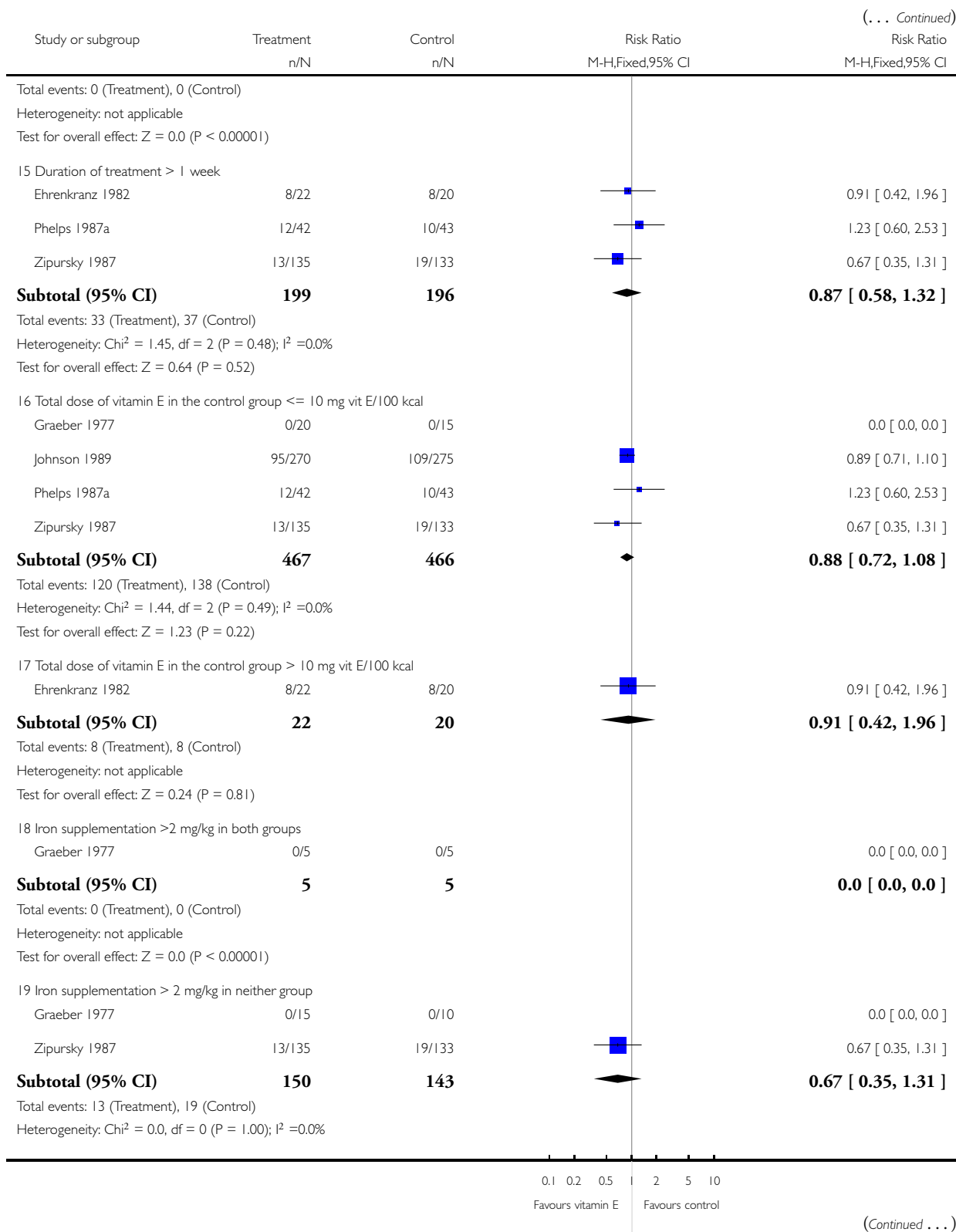
Outcome: 32 Retrolental fibroplasia/retinopathy of prematurity among very low birth weight infants

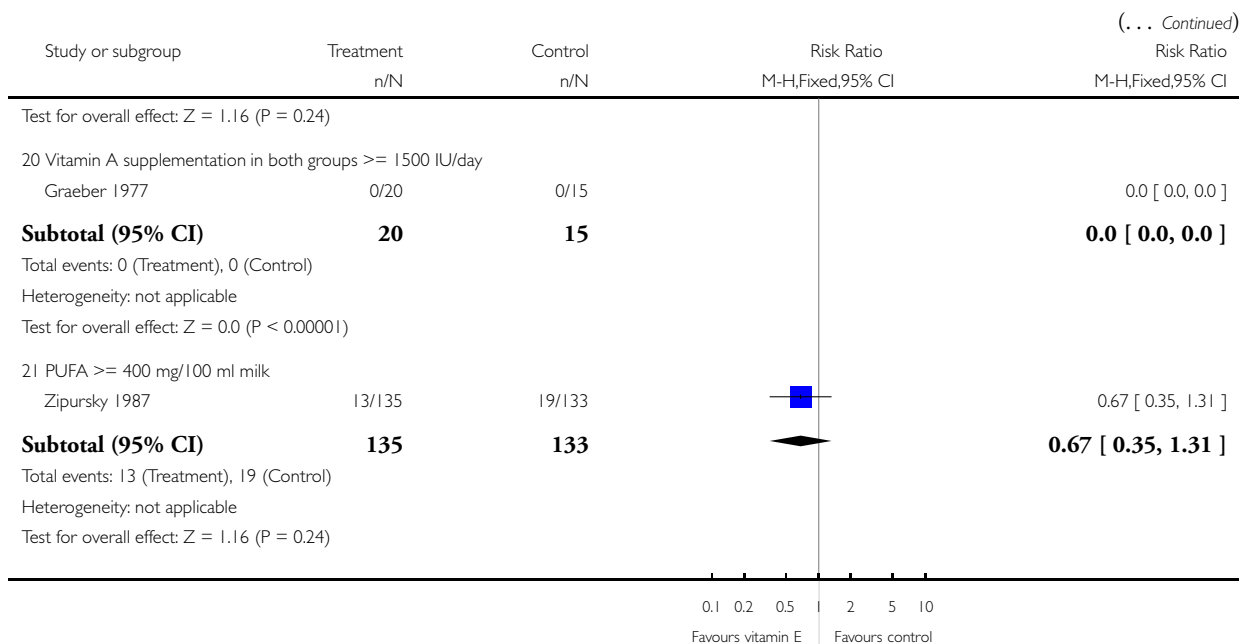










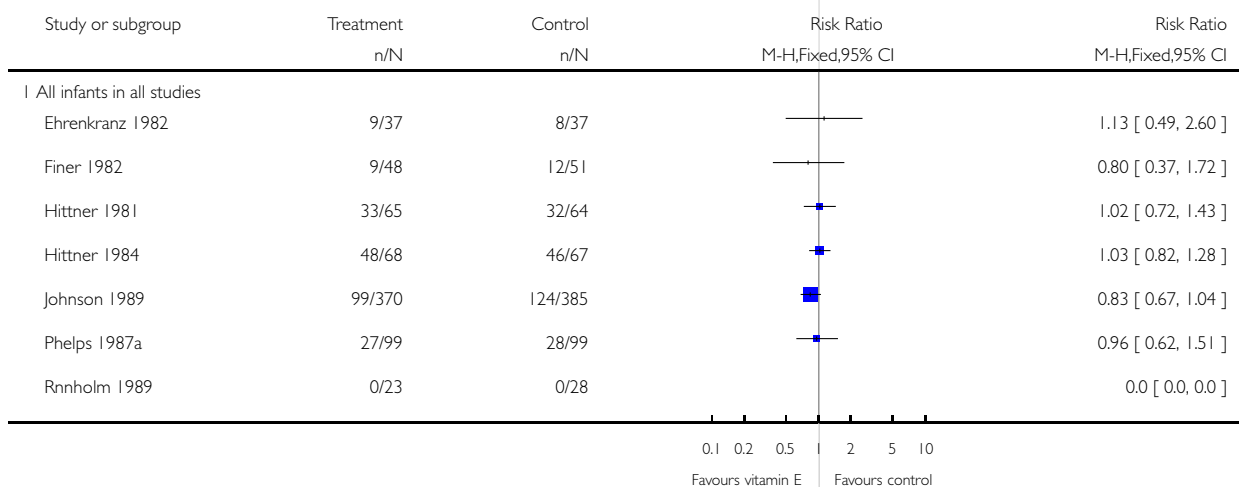


### Analysis 1.33. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 33 Retrolental fibroplasia/retinopathy of prematurity among infants examined/survivors.

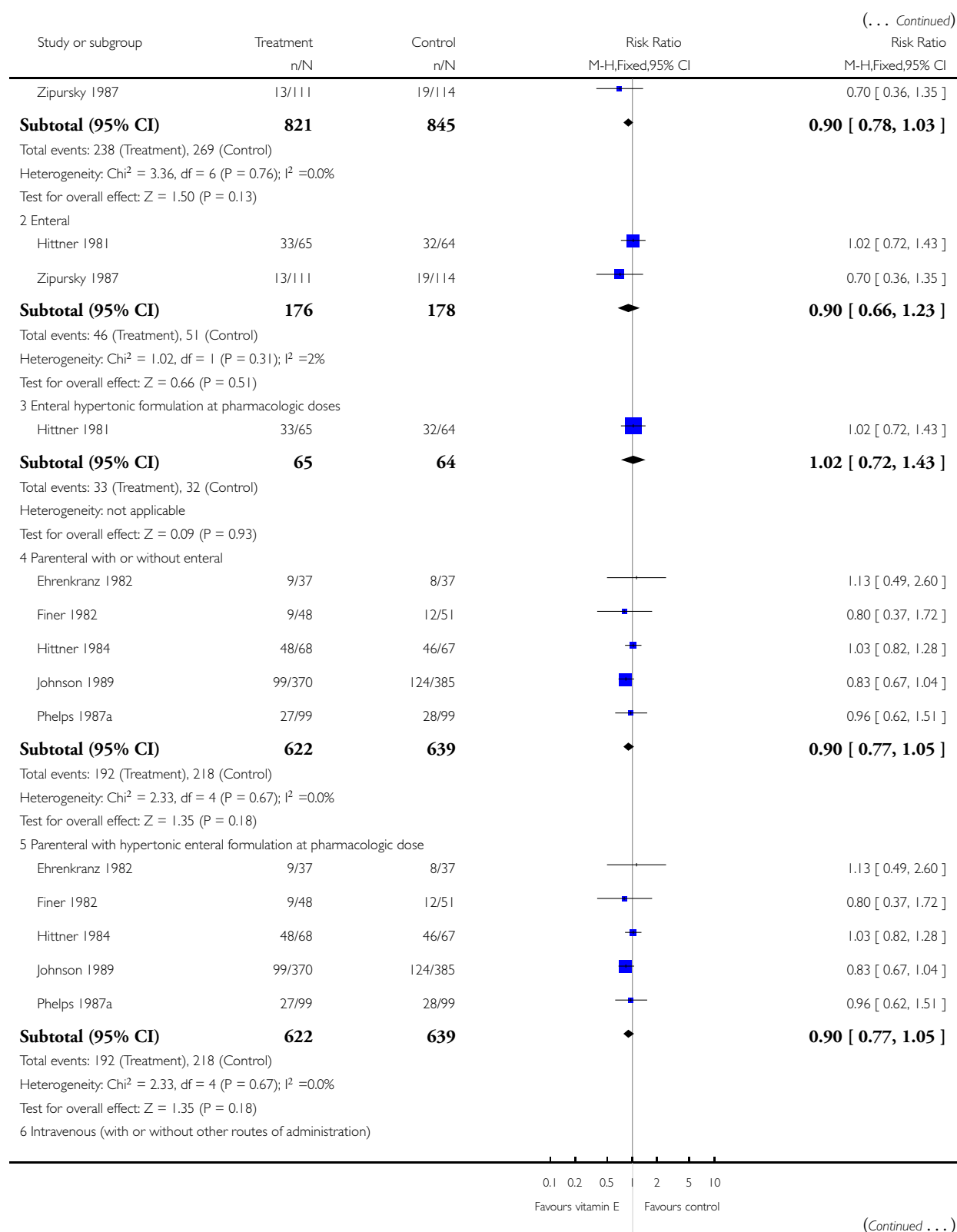
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

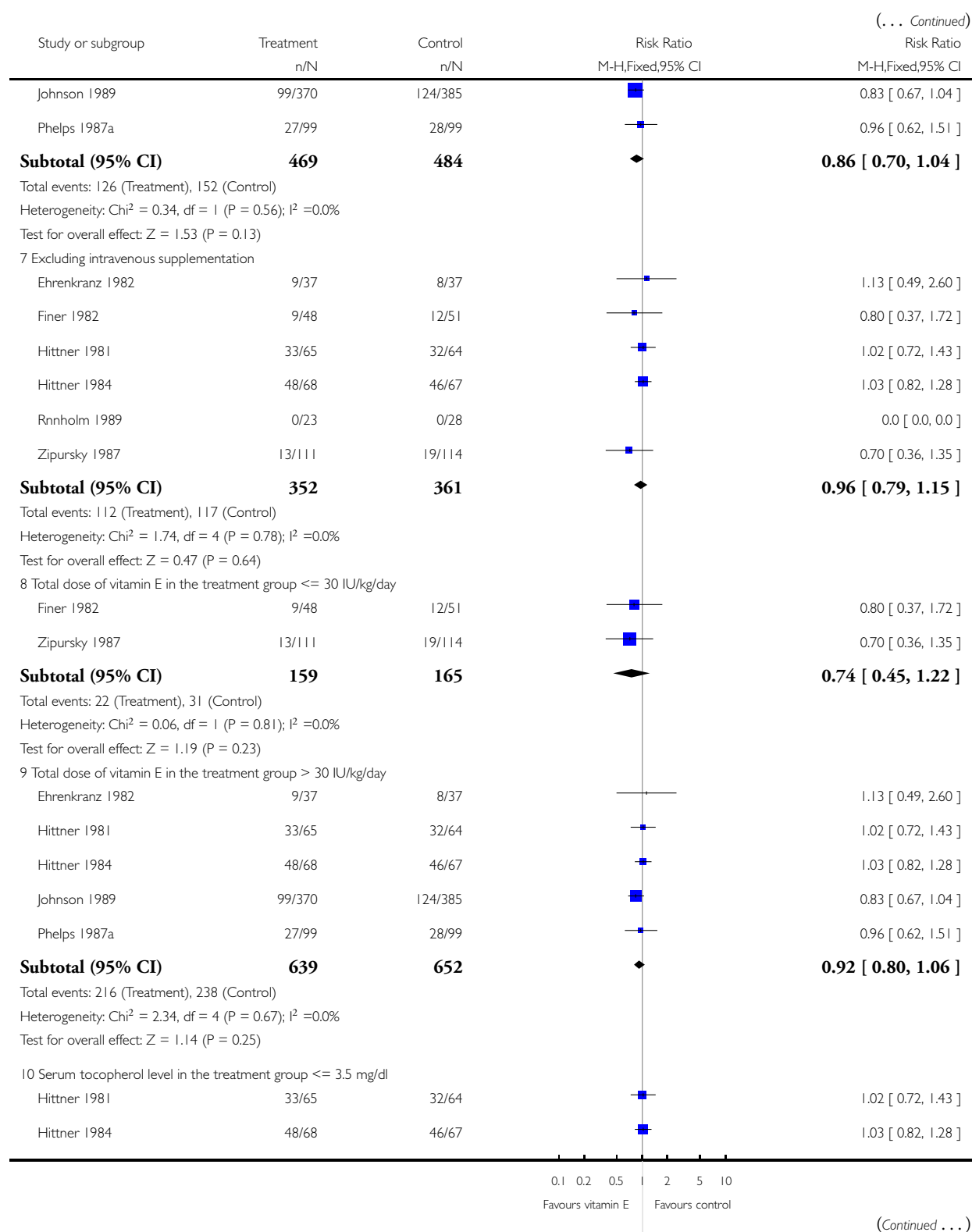
Comparison: 1 Vitamin E versus placebo or no vitamin E

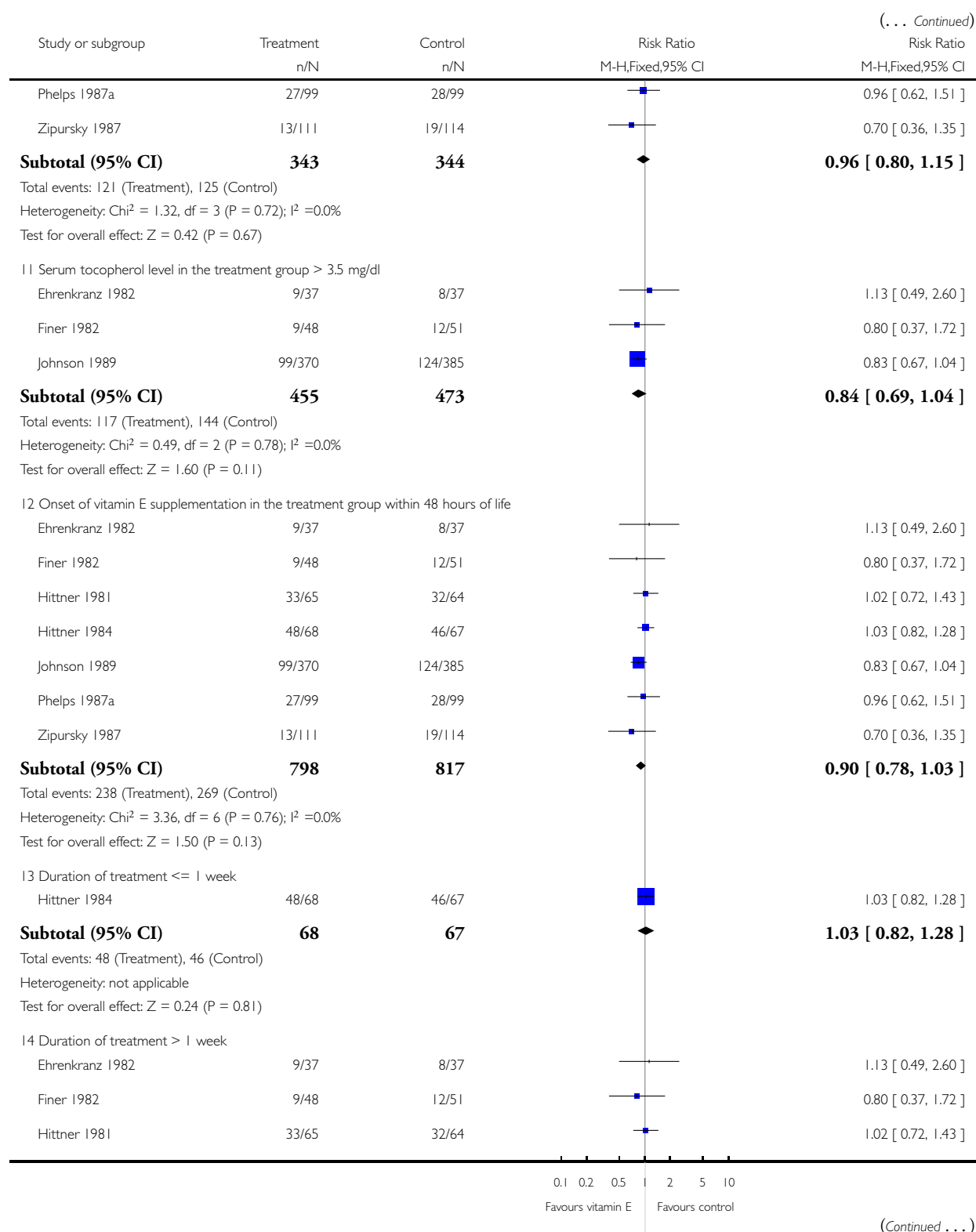
Outcome: 33 Retrolental fibroplasia/retinopathy of prematurity among infants examined/survivors

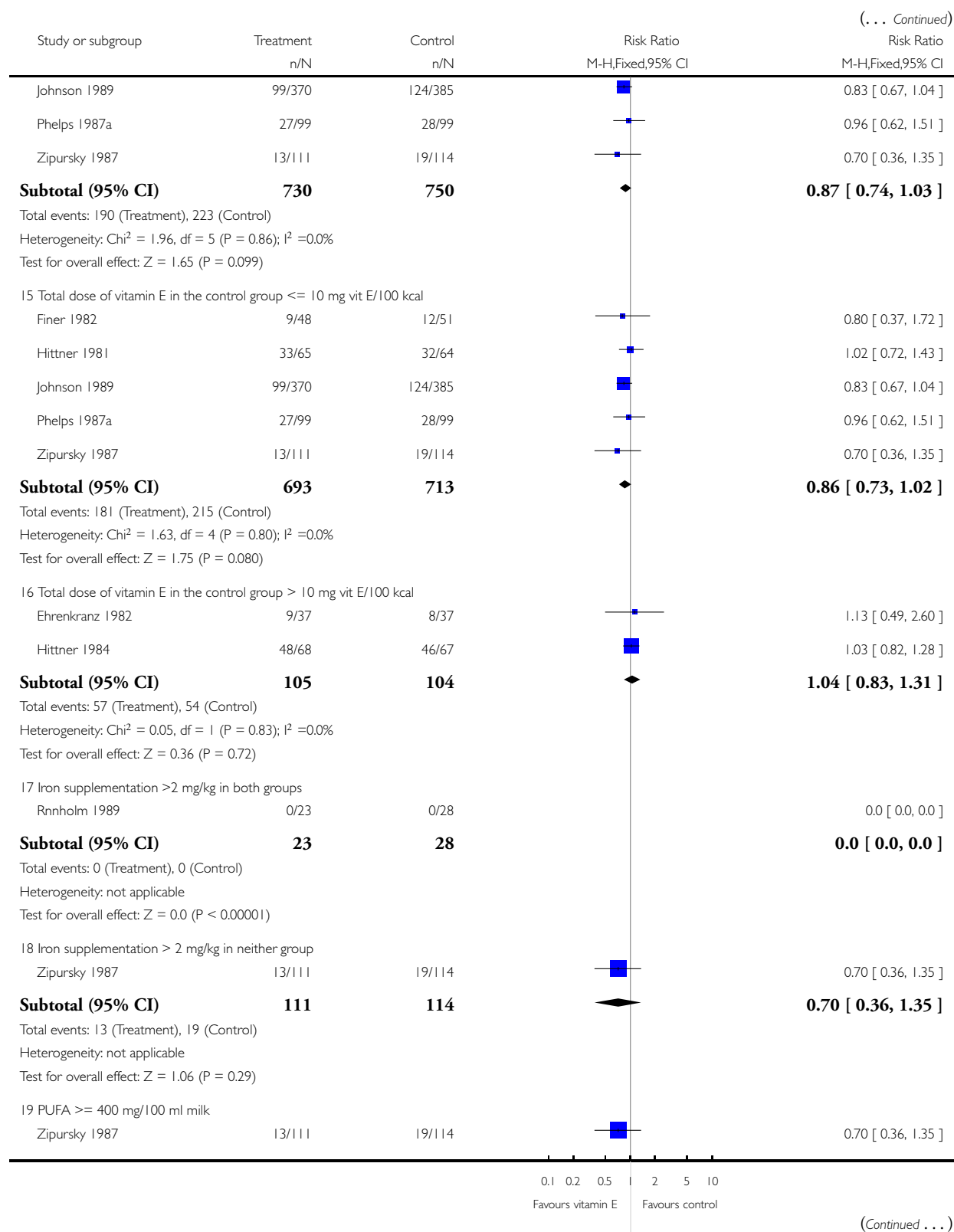


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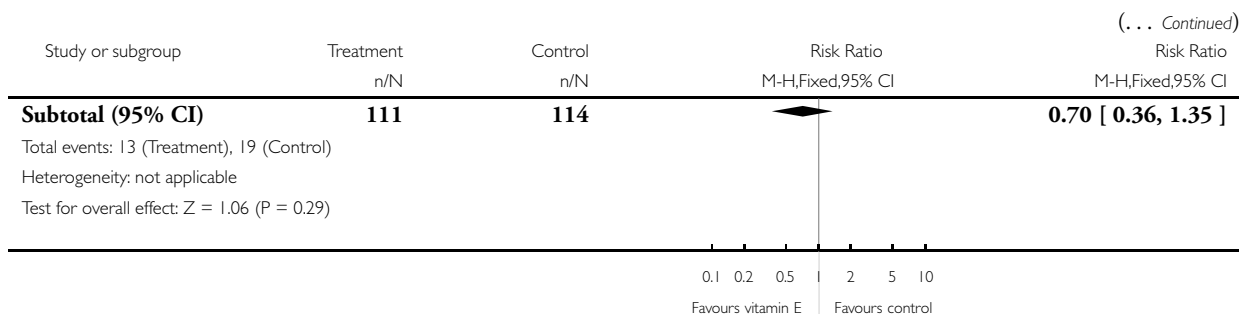










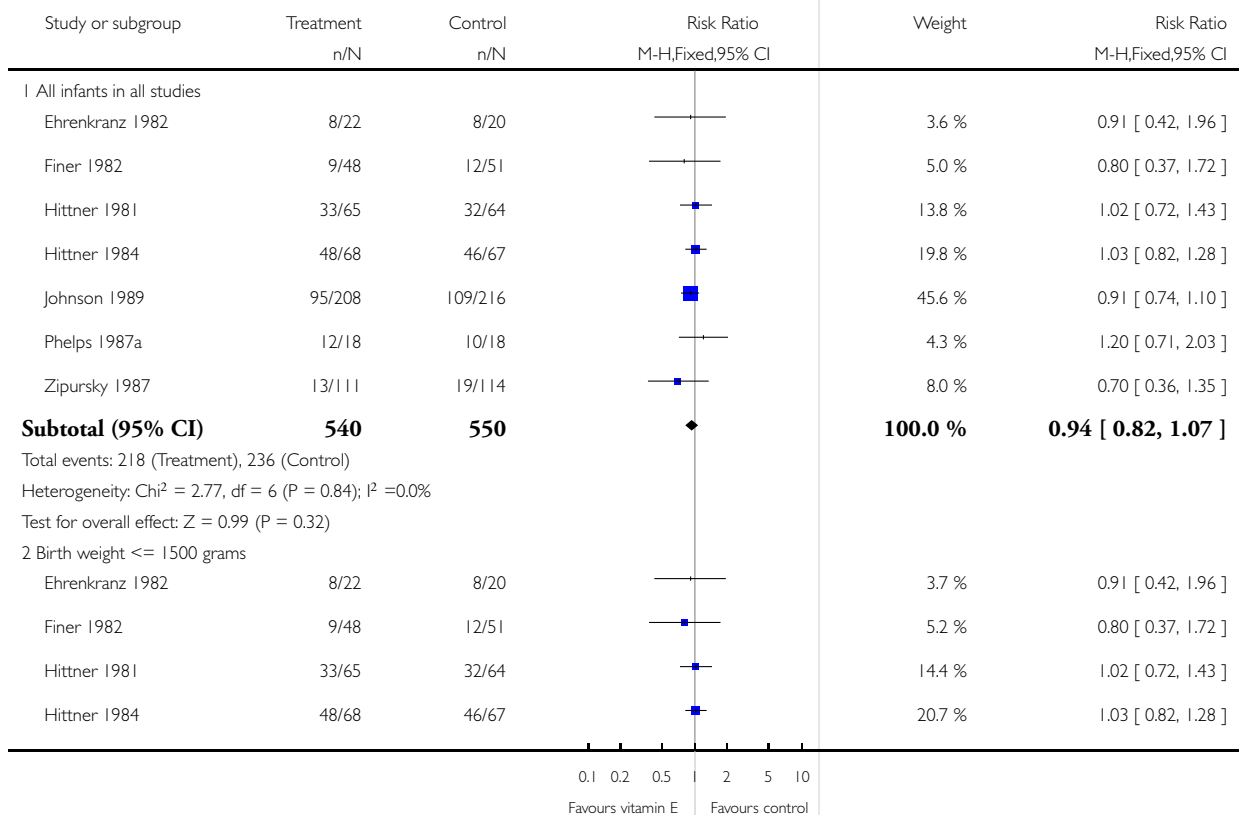


### Analysis 1.34. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 34 Retrolental fibroplasia/retinopathy of prematurity among very low birth weight infants examined.

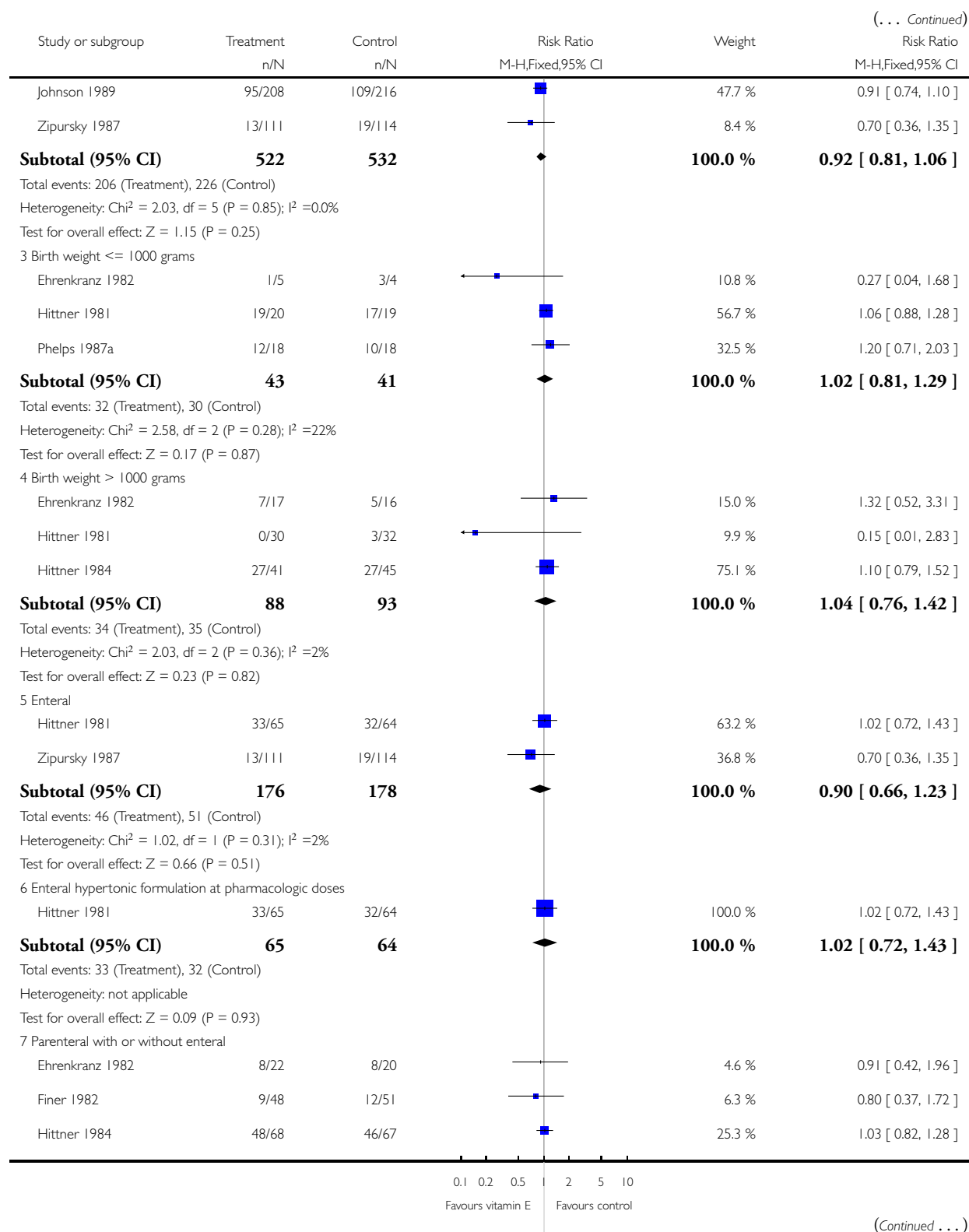
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

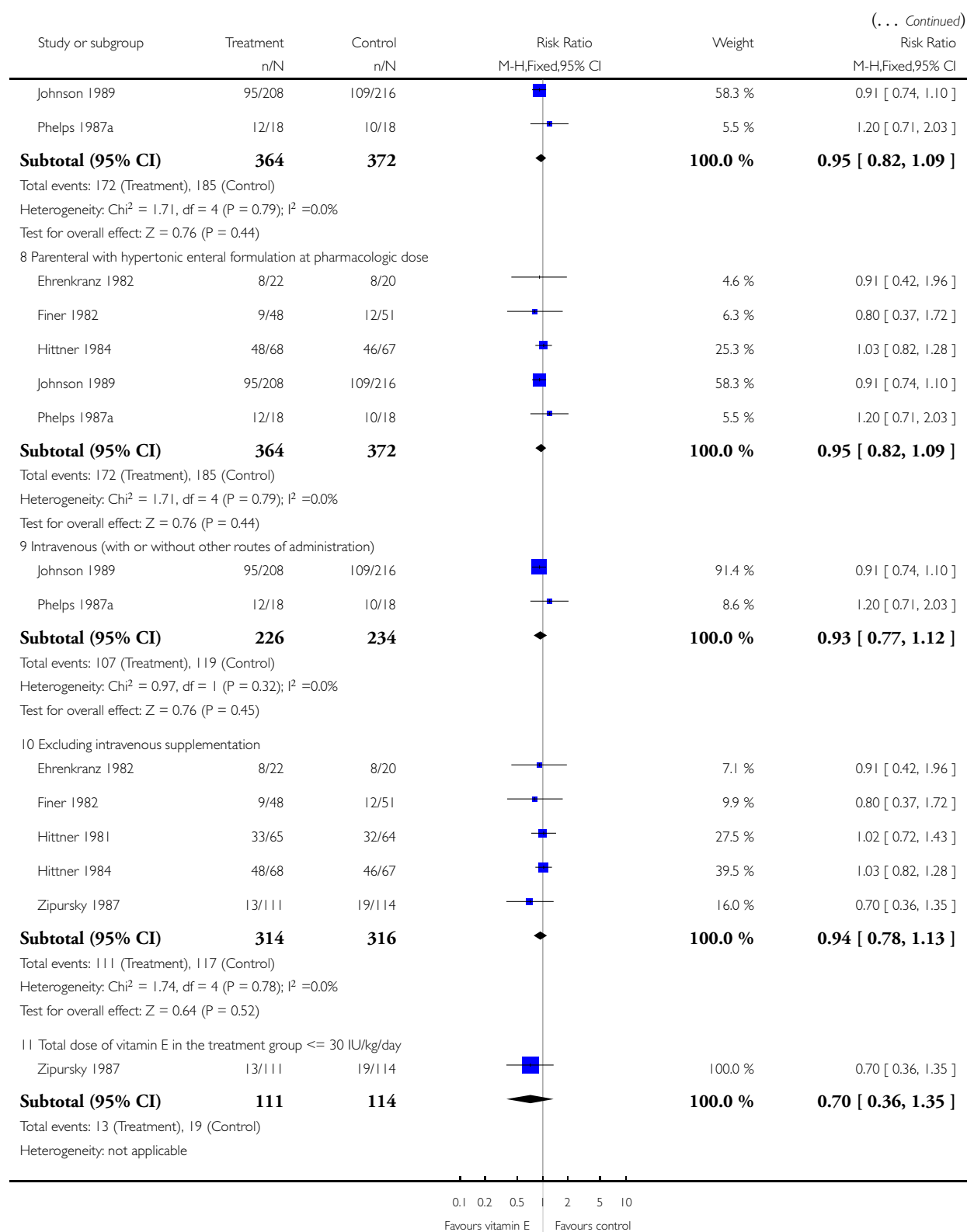
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 34 Retrolental fibroplasia/retinopathy of prematurity among very low birth weight infants examined

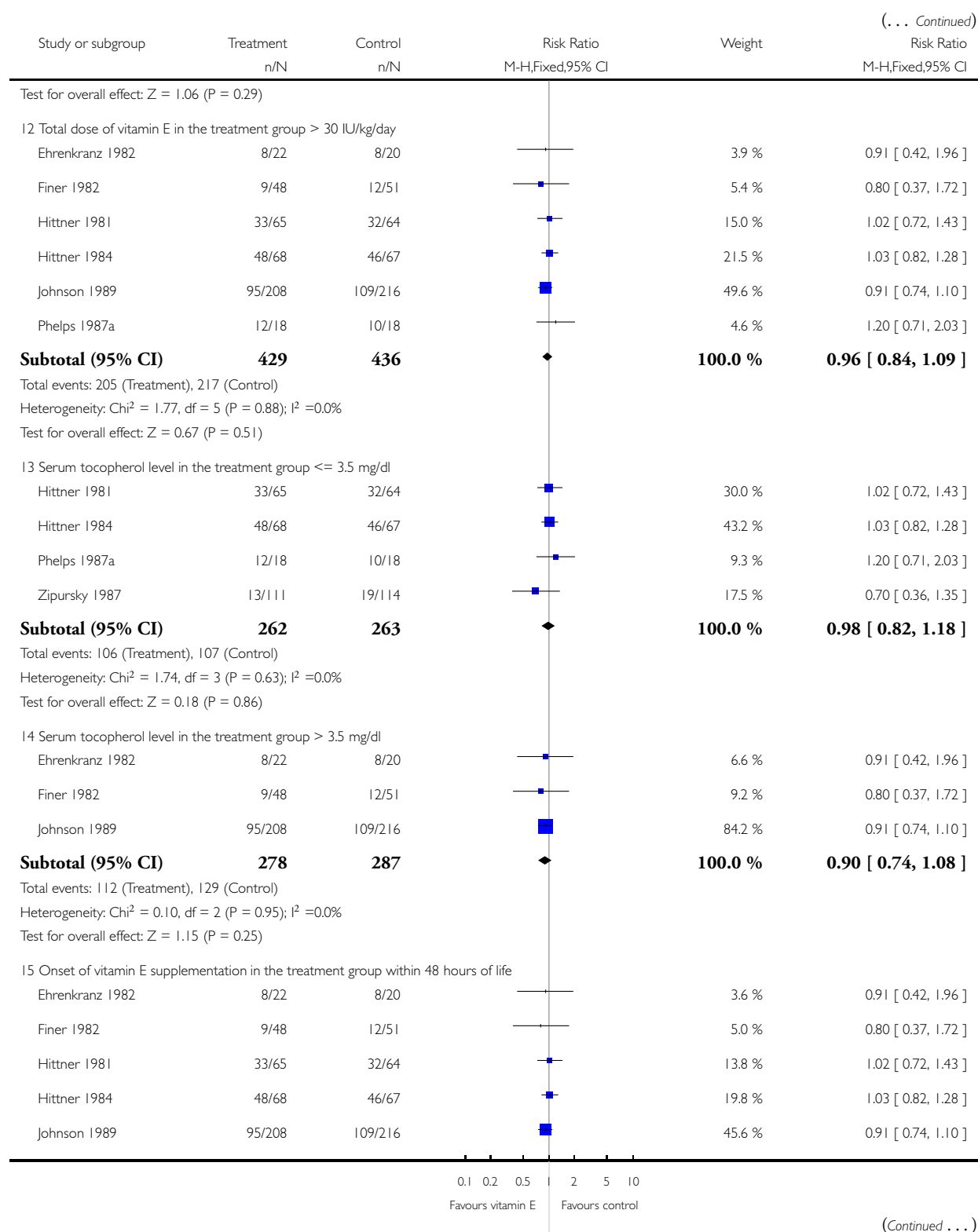


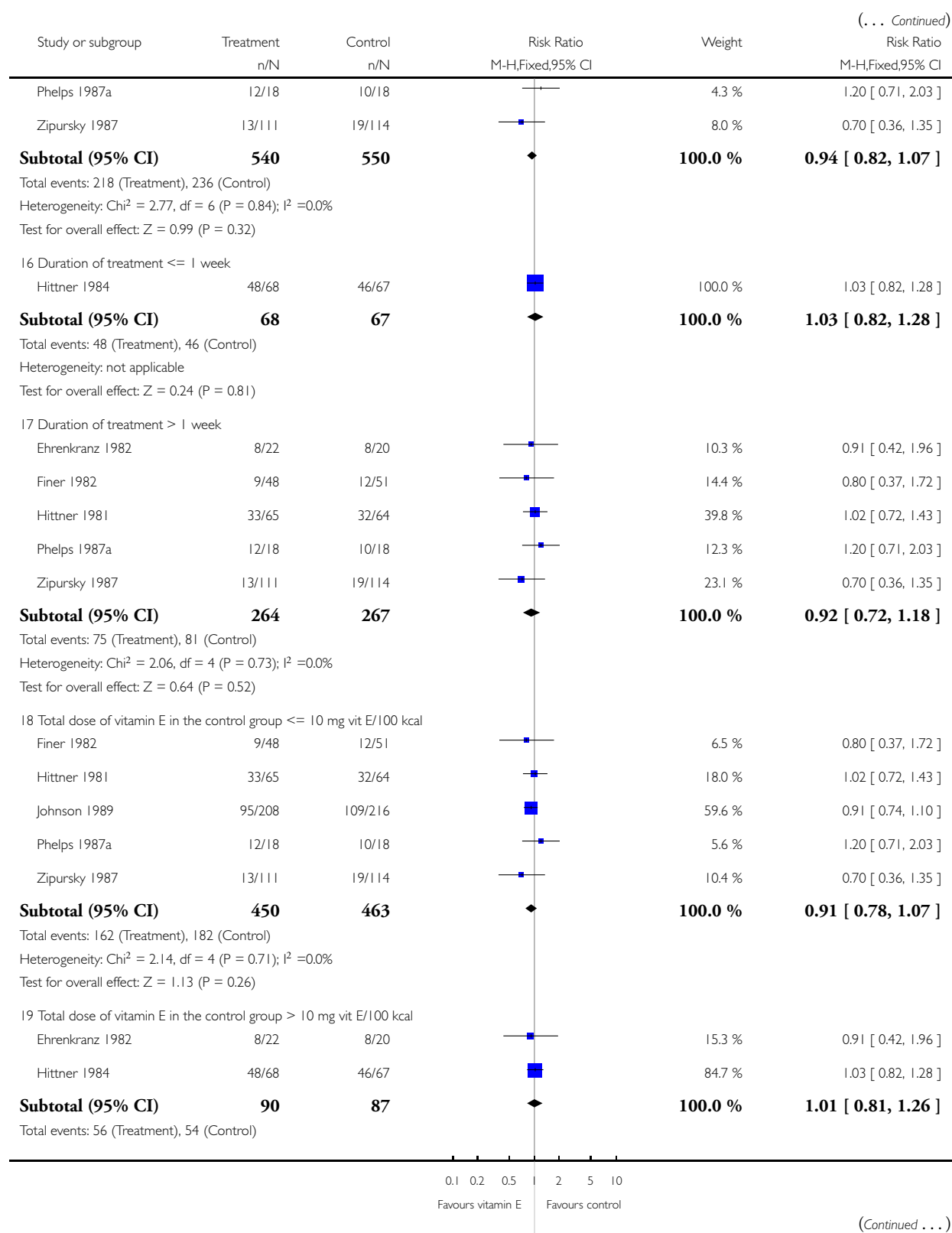
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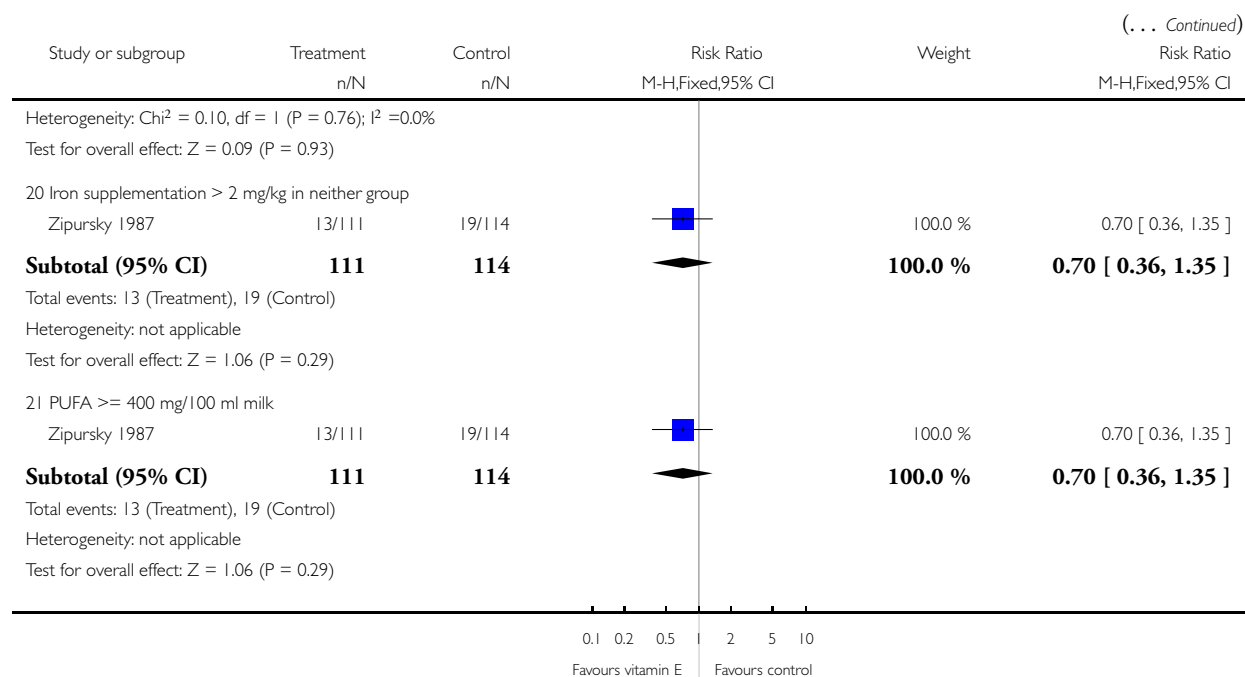




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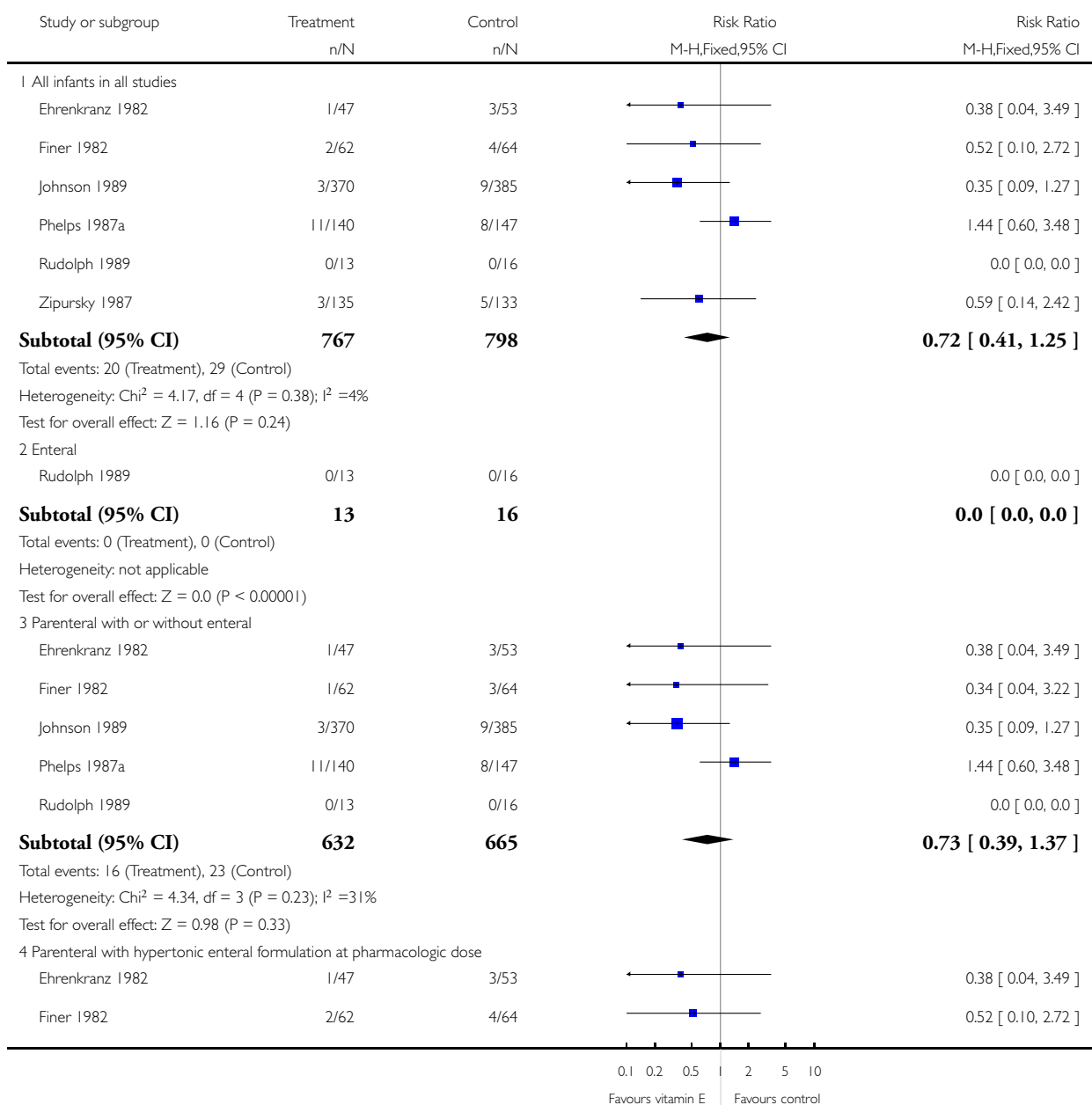


### Analysis 1.35. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 35 Severe retrolental fibroplasia/retinopathy of prematurity (grade 3 or worse).

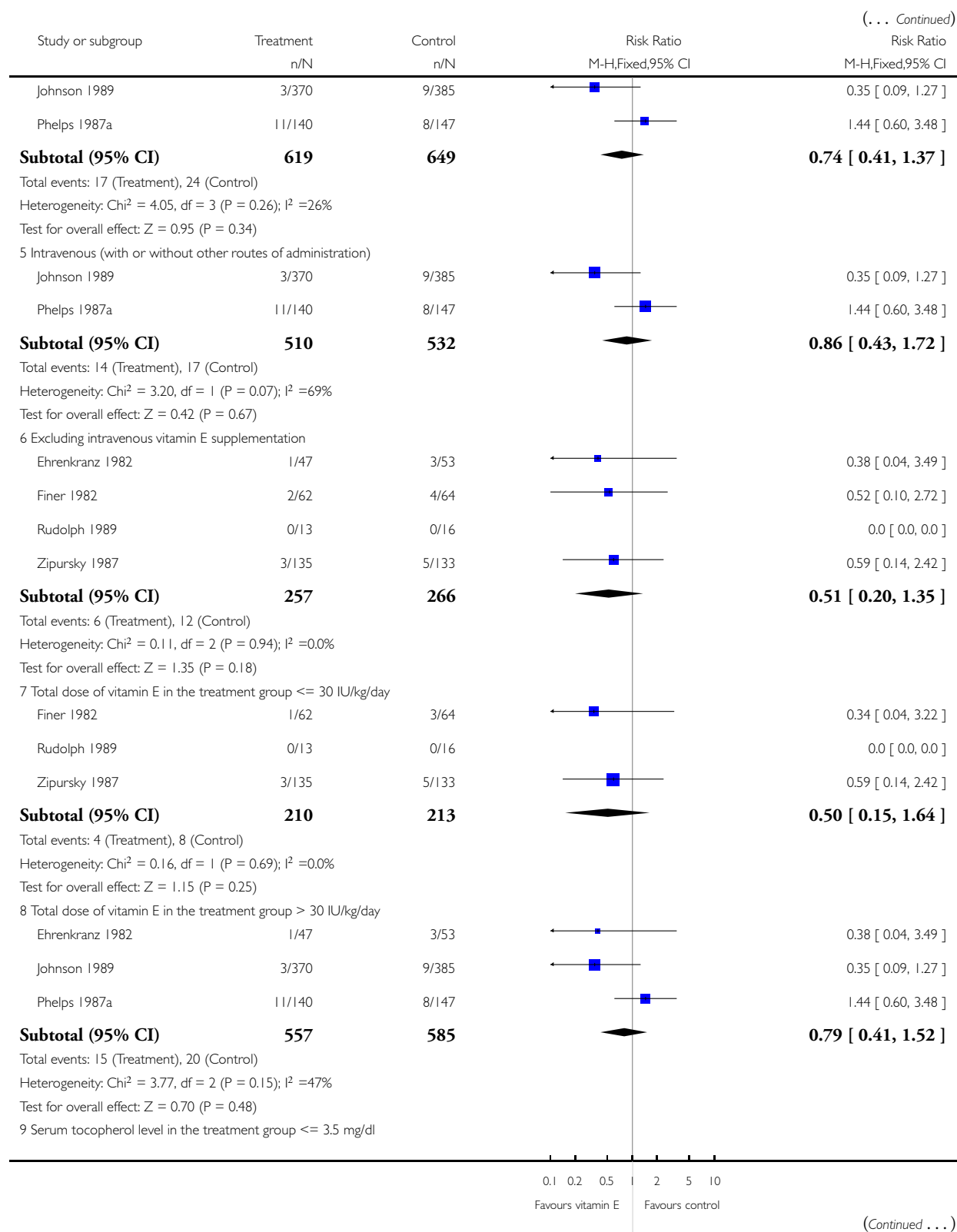
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

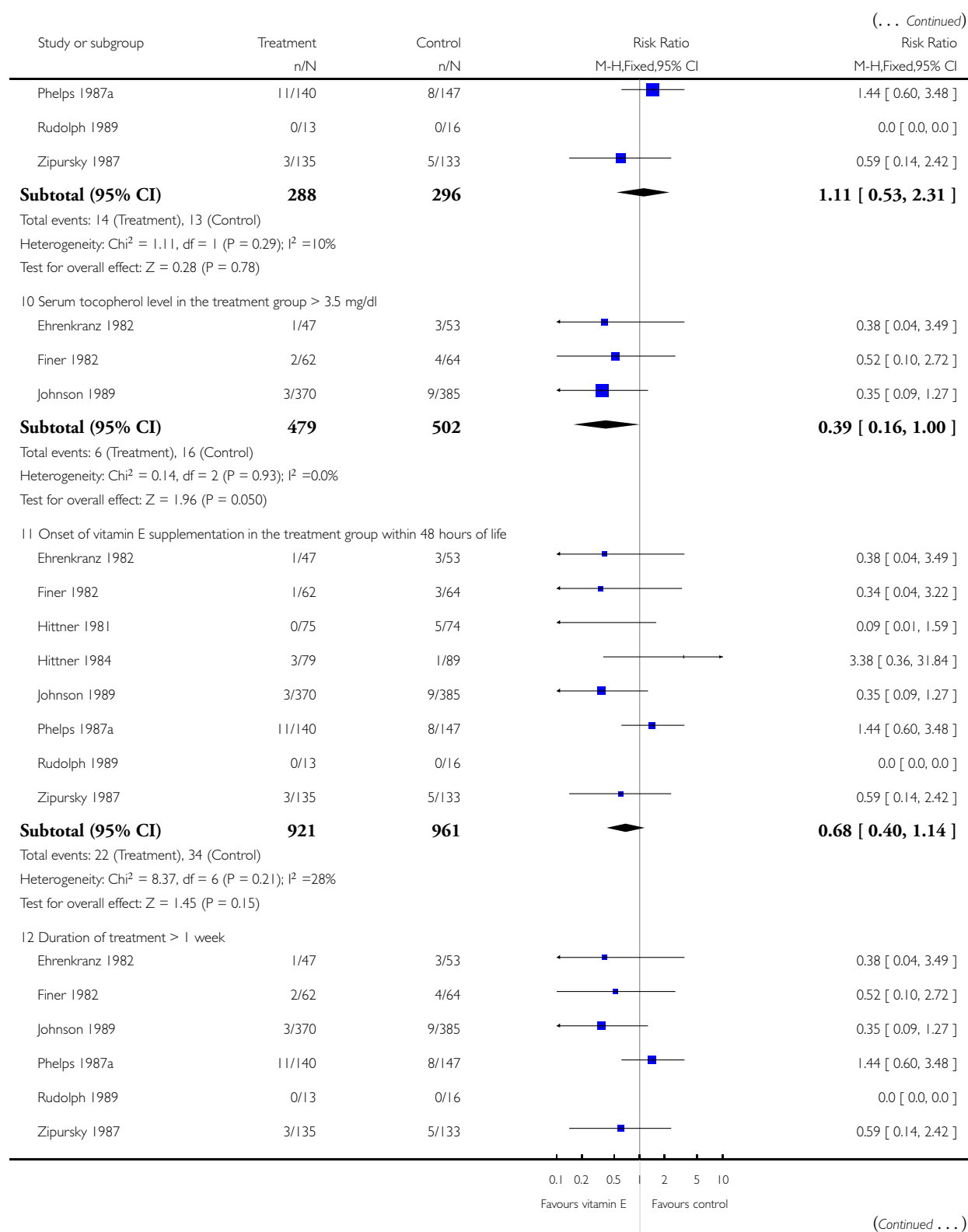
Outcome: 35 Severe retrolental fibroplasia/retinopathy of prematurity (grade 3 or worse)

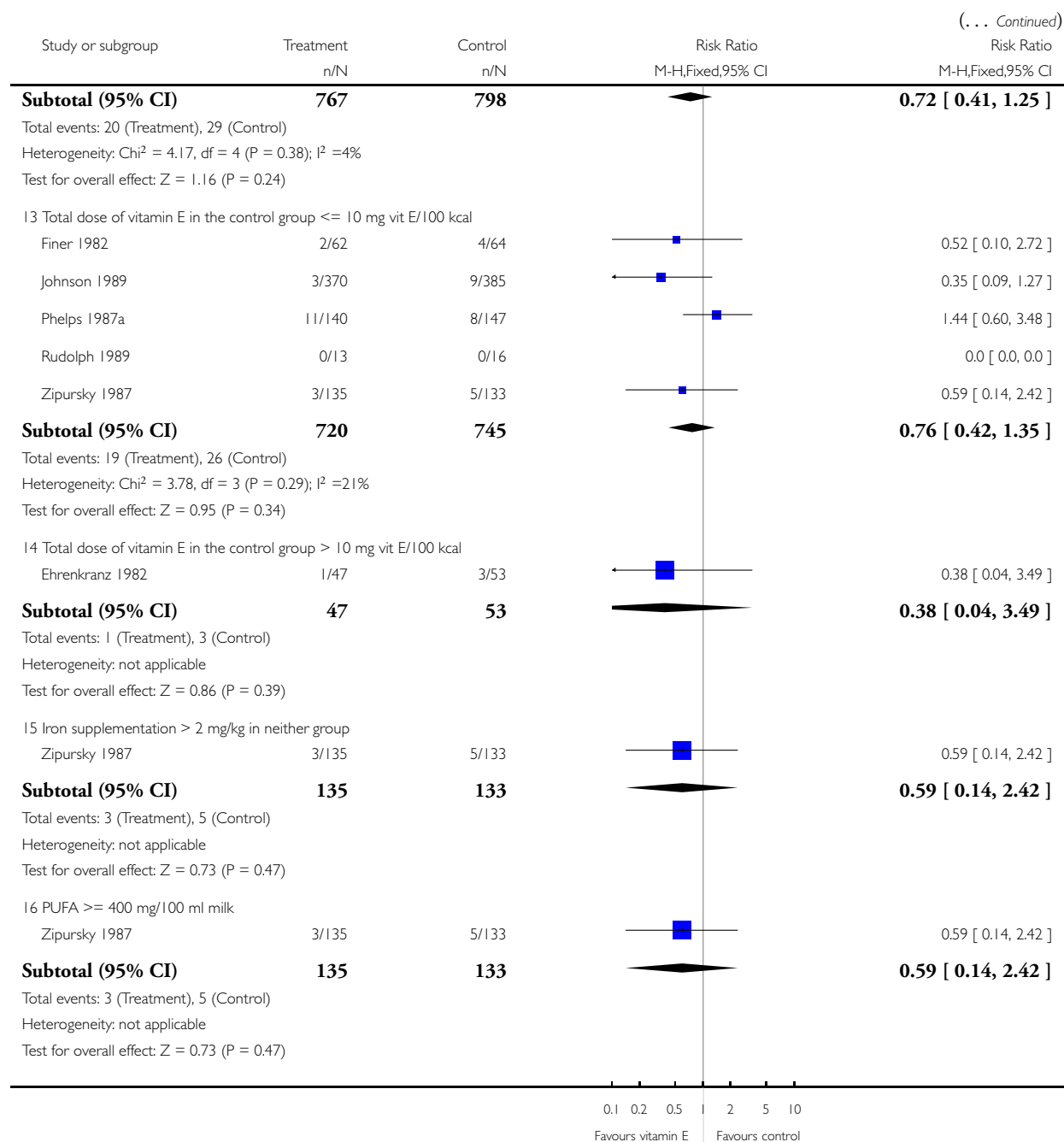


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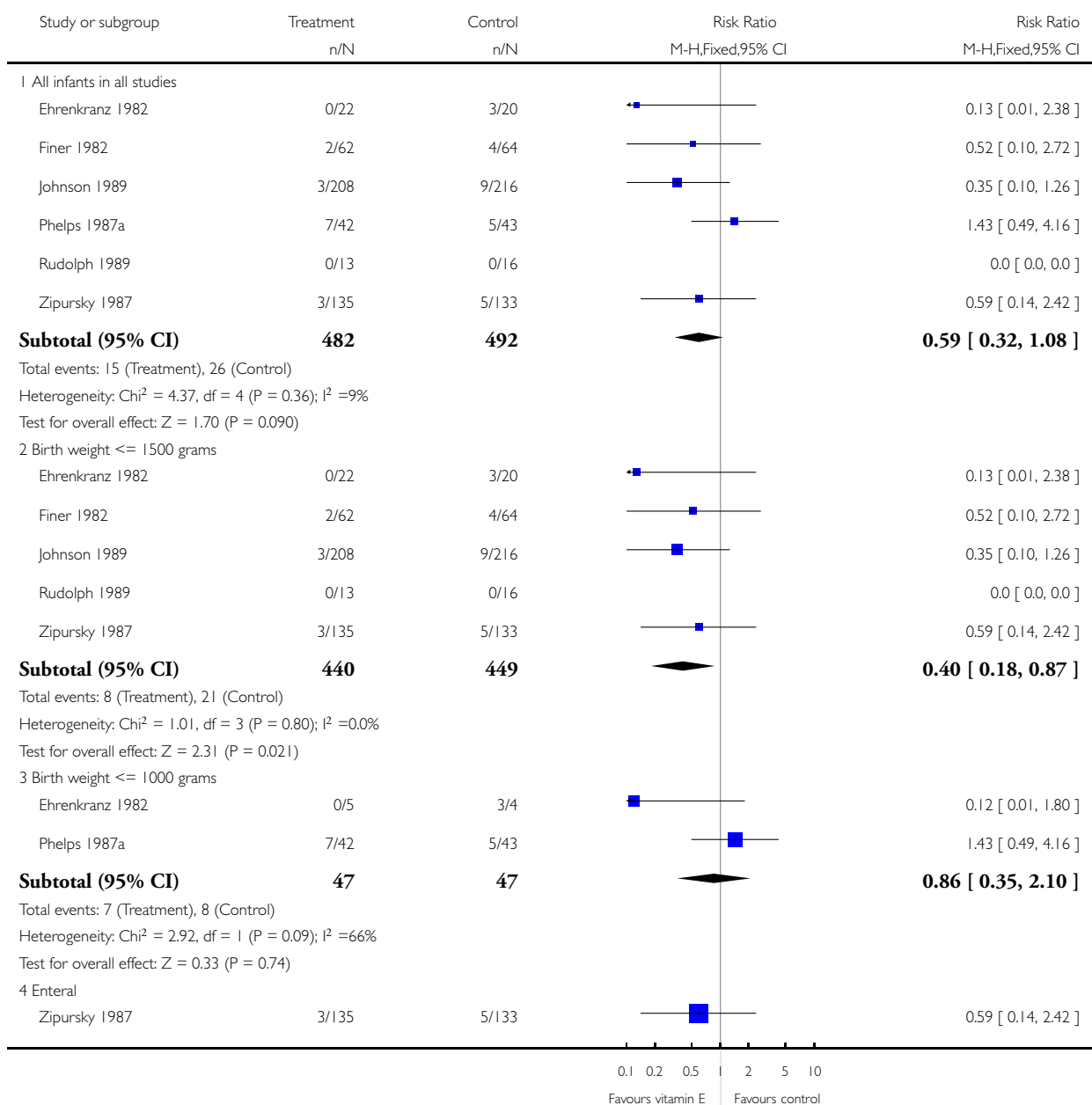


### Analysis 1.36. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 36 Severe retrolental fibroplasia/retinopathy of prematurity (grade $\geq 3$ ) among very low birth weight infants.

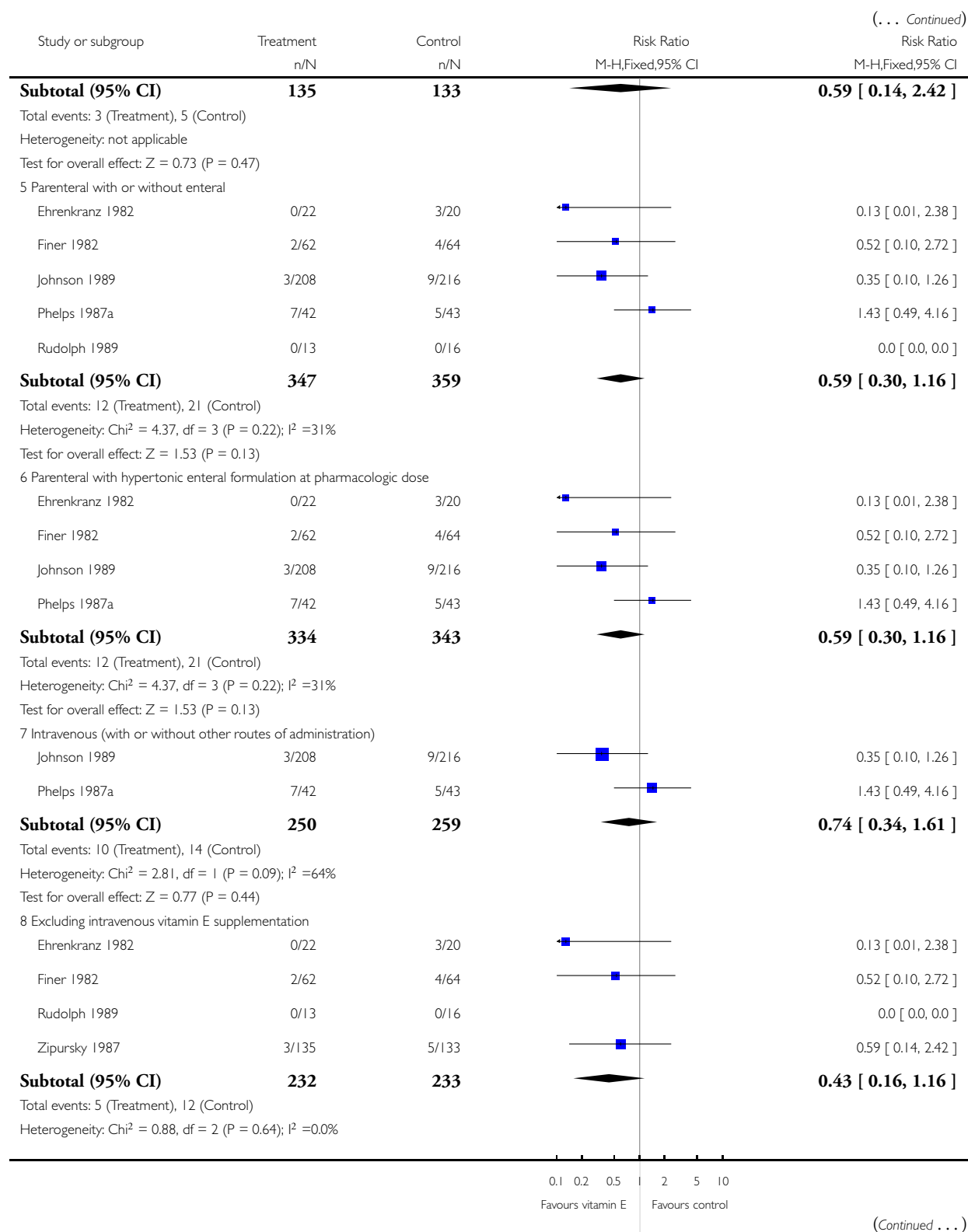
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

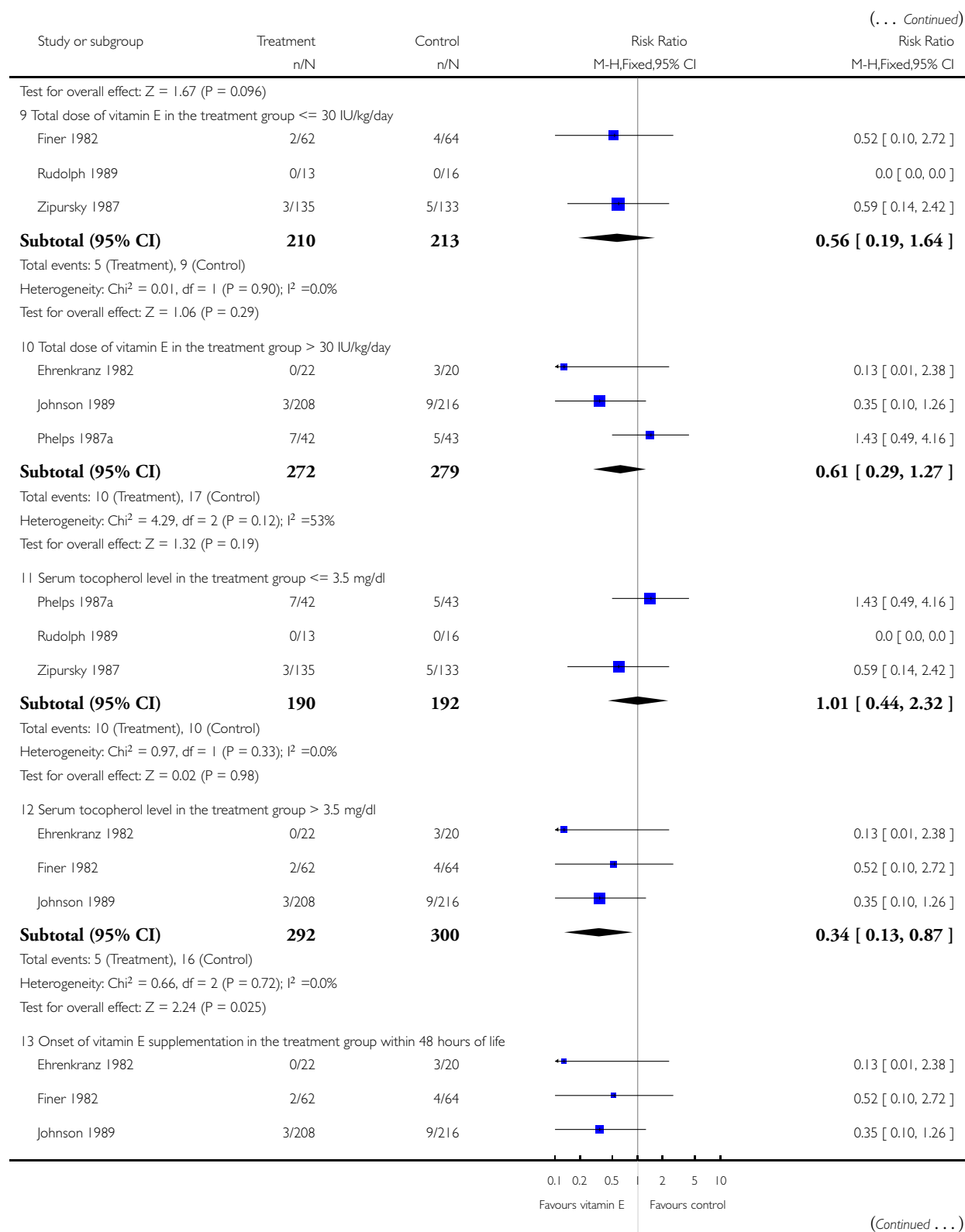
Comparison: 1 Vitamin E versus placebo or no vitamin E

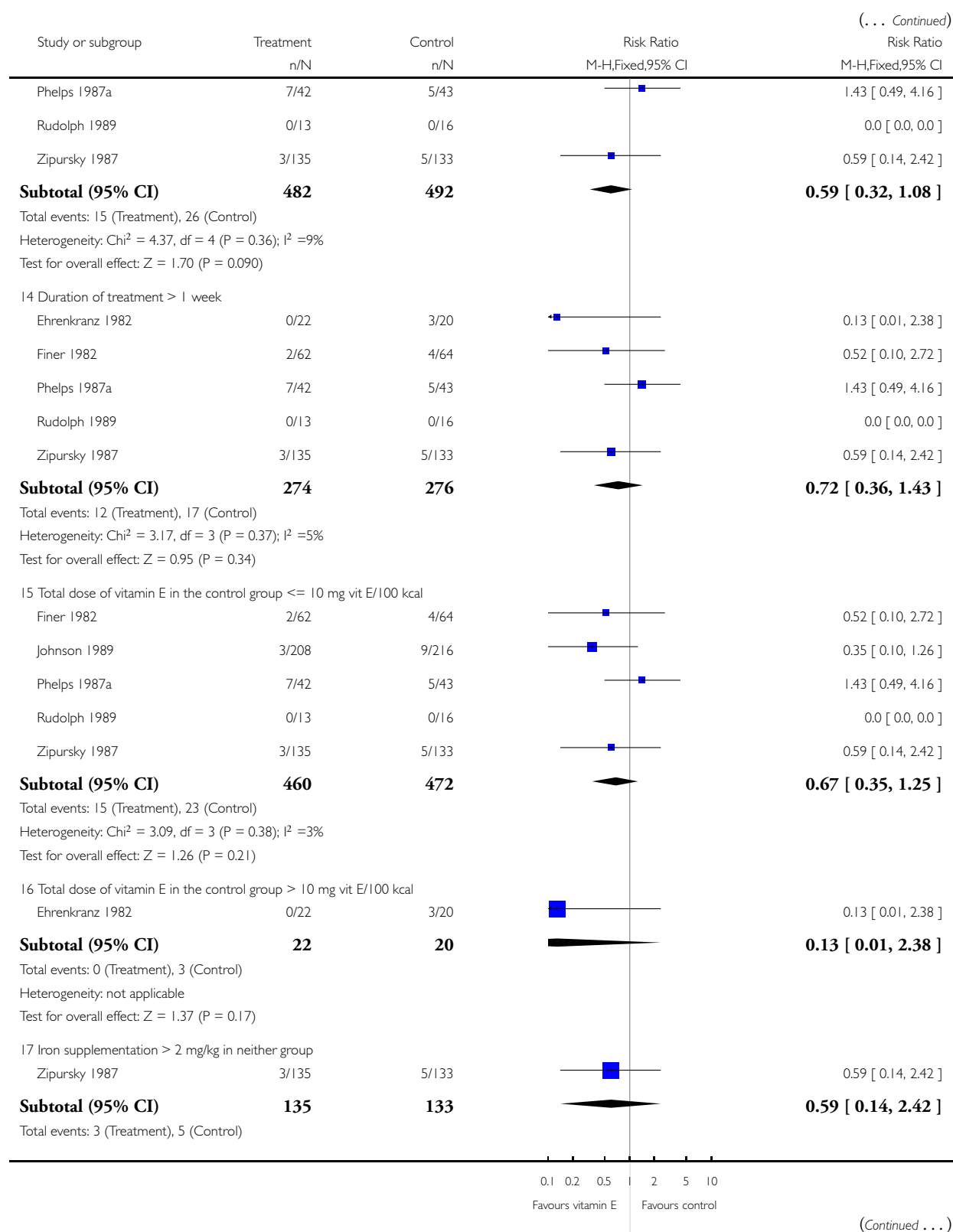
Outcome: 36 Severe retrolental fibroplasia/retinopathy of prematurity (grade  $\geq 3$ ) among very low birth weight infants

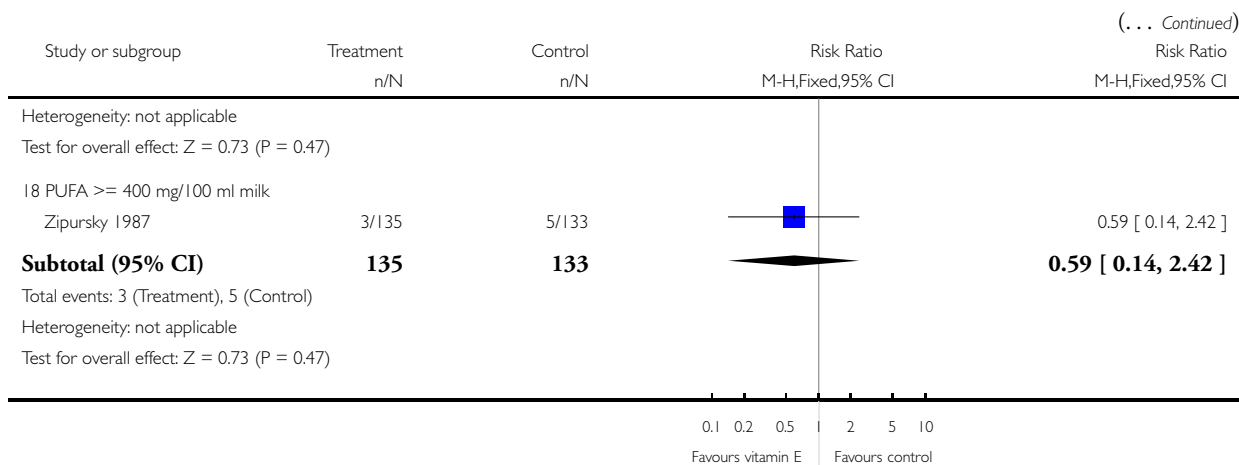


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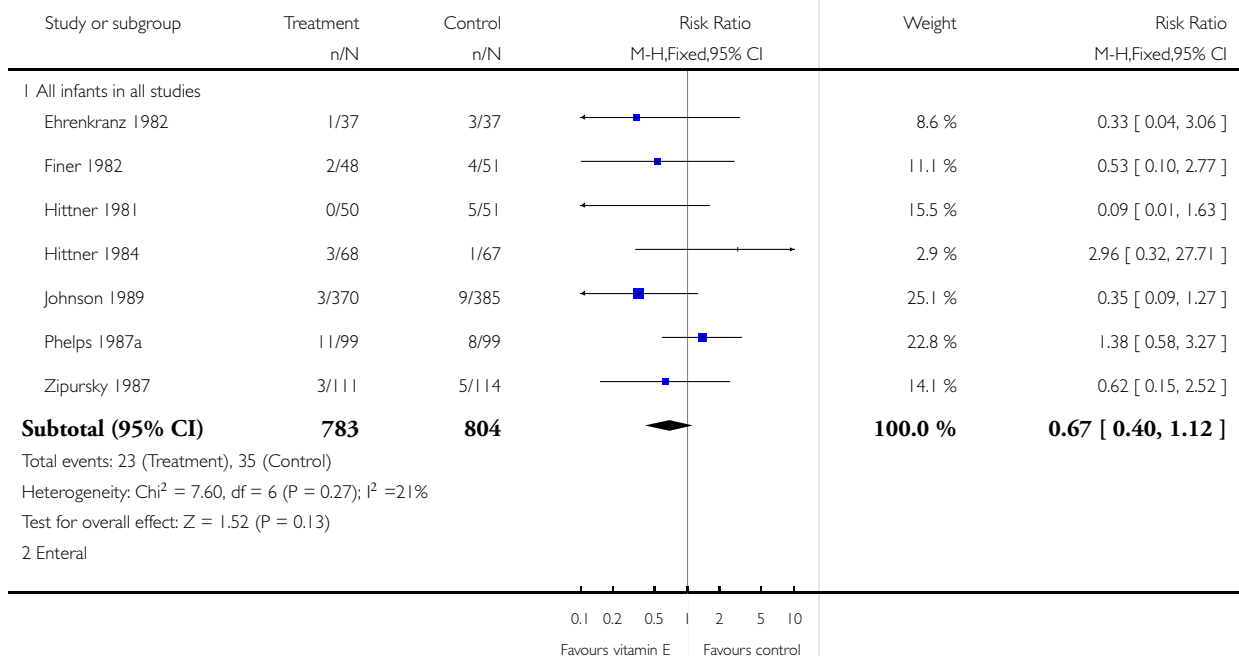


**Analysis 1.37. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 37 Severe retrolental fibroplasia/retinopathy of prematurity (grade 3 or worse) among patients examined.**

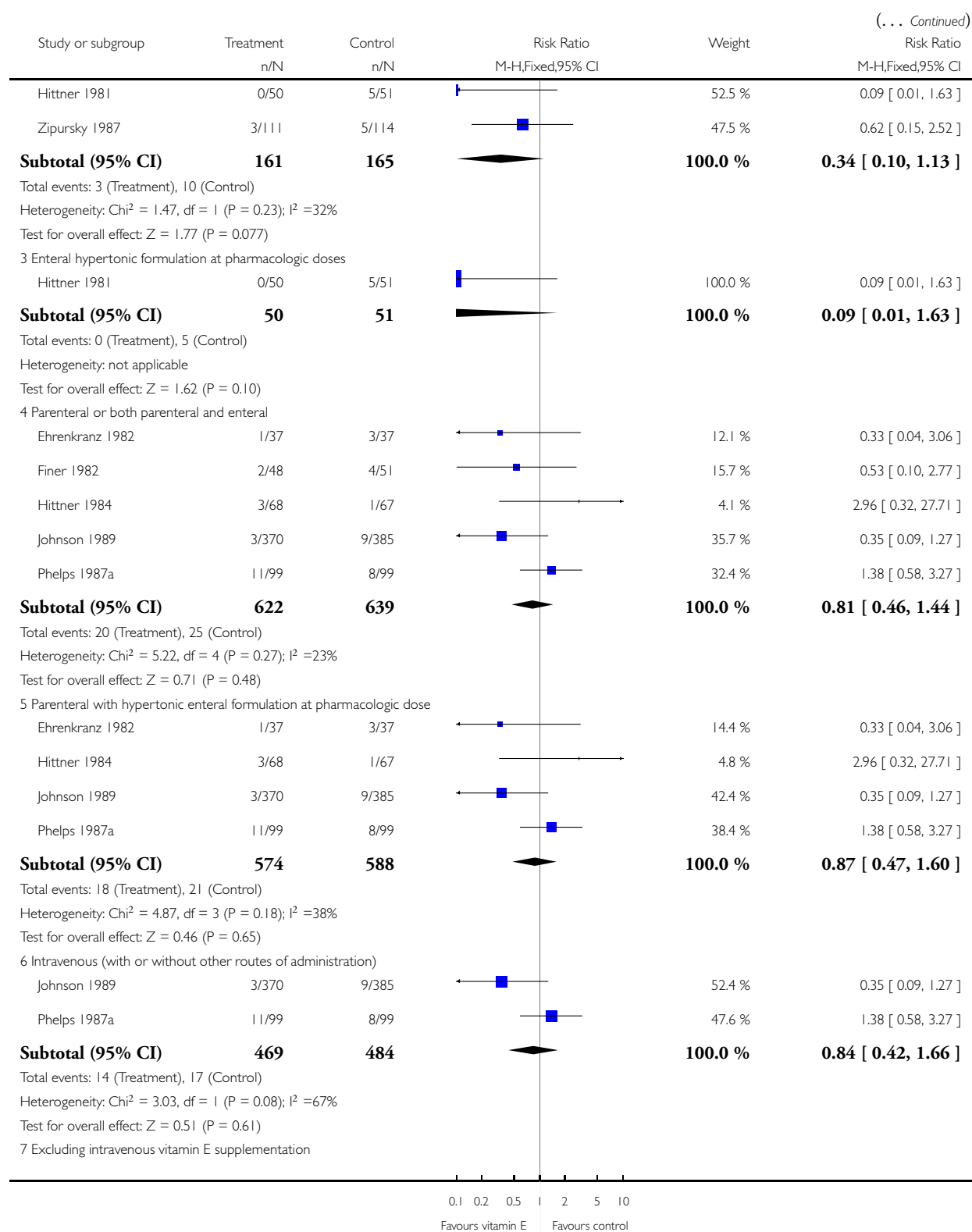
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

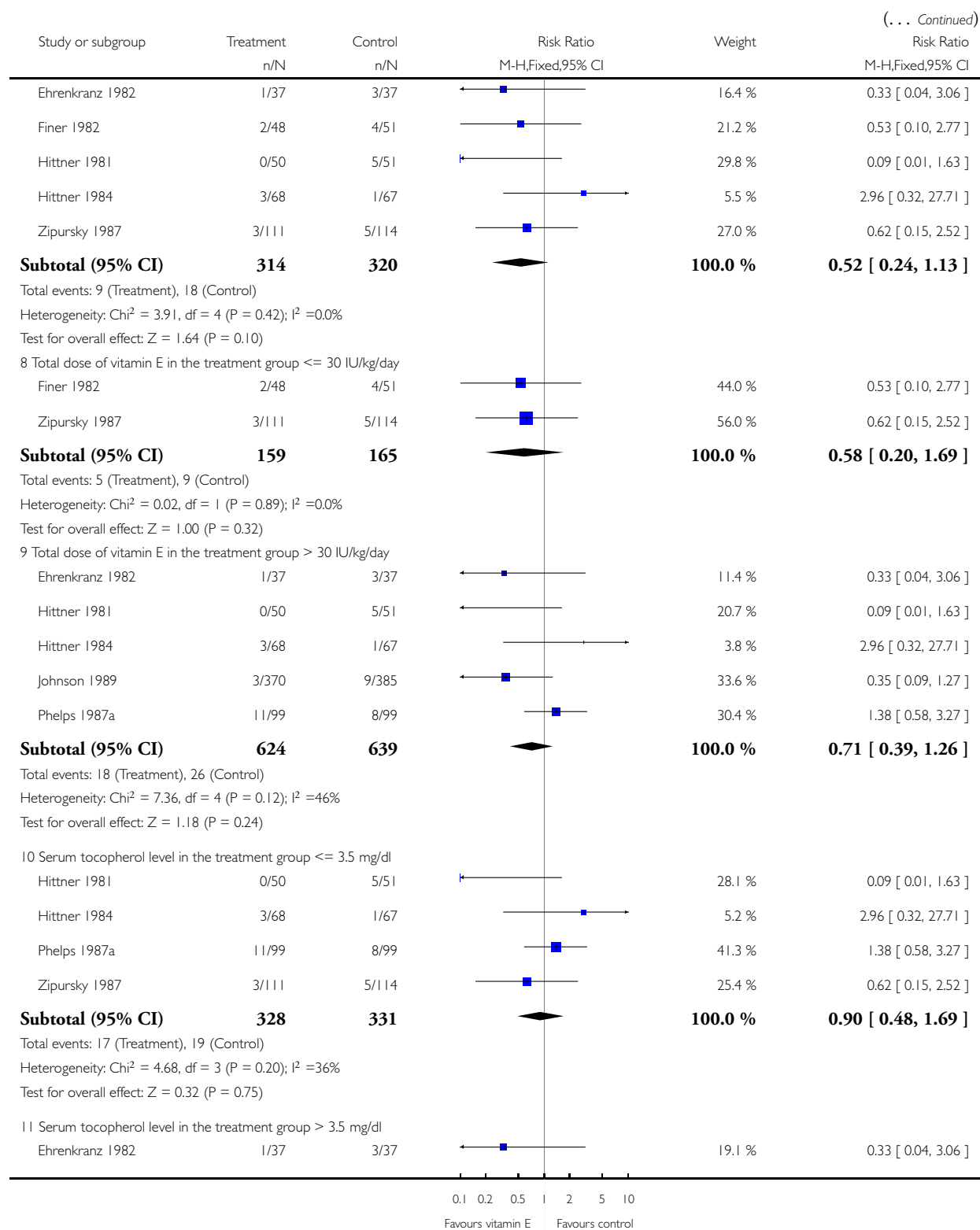
Outcome: 37 Severe retrolental fibroplasia/retinopathy of prematurity (grade 3 or worse) among patients examined



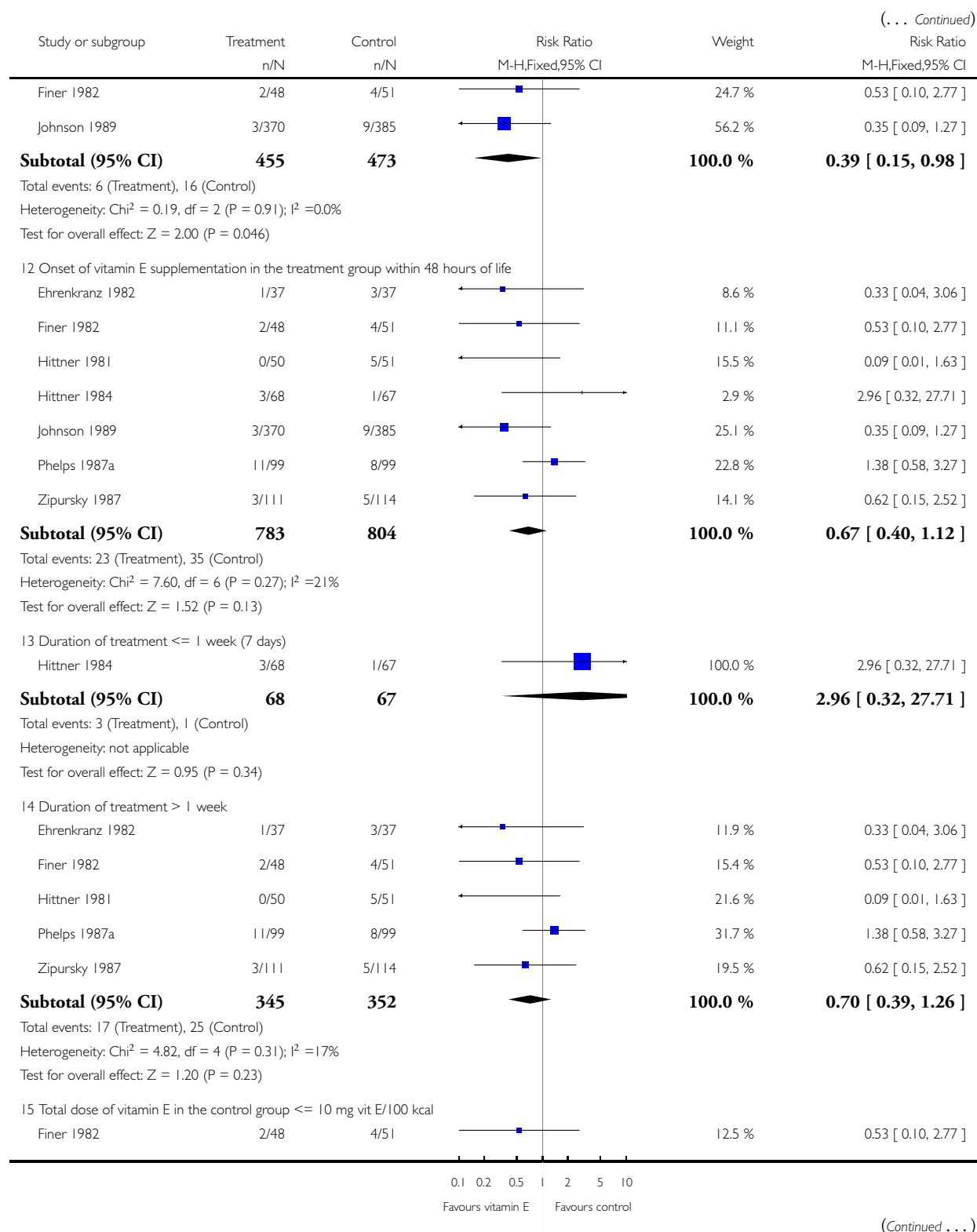
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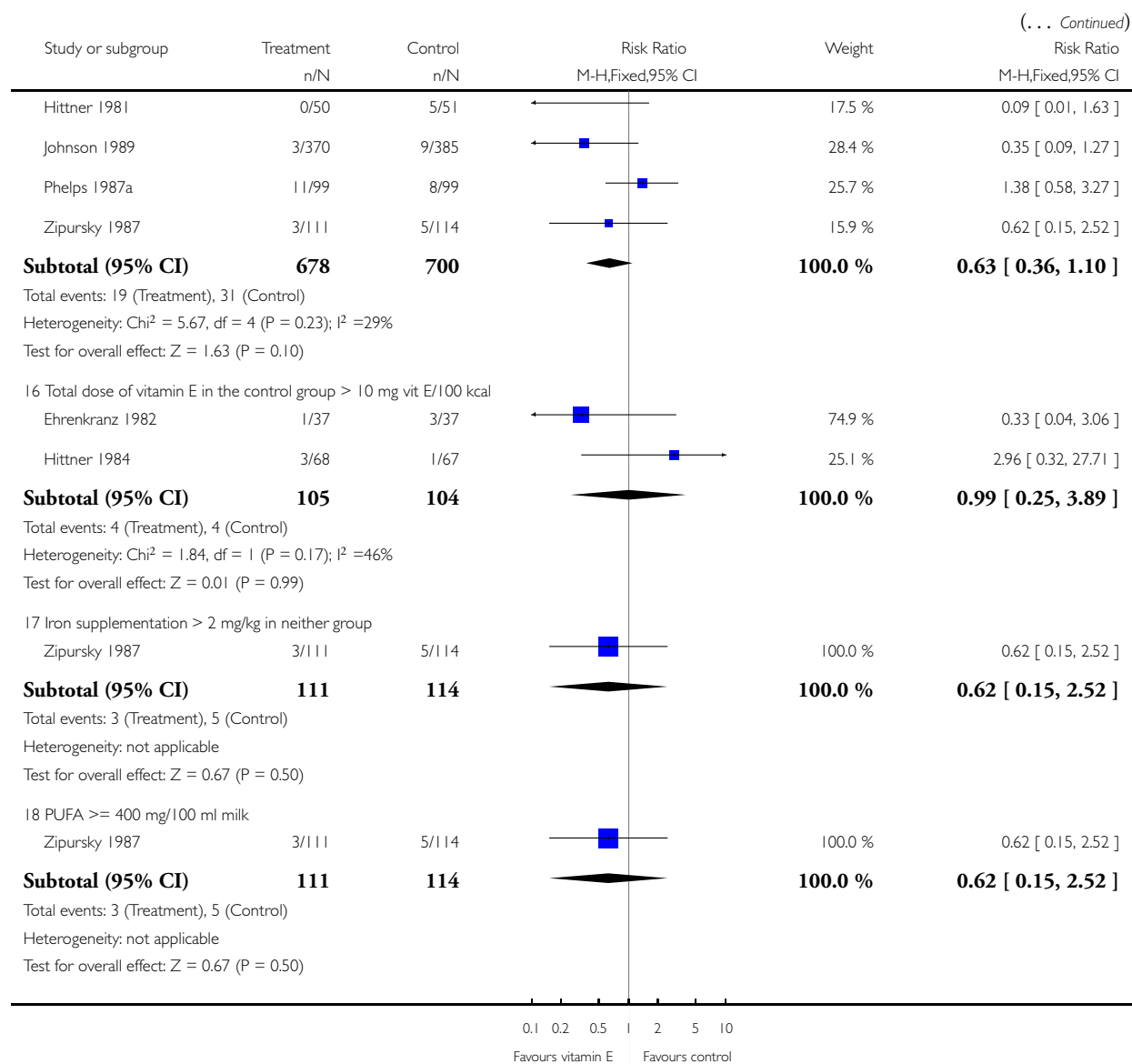






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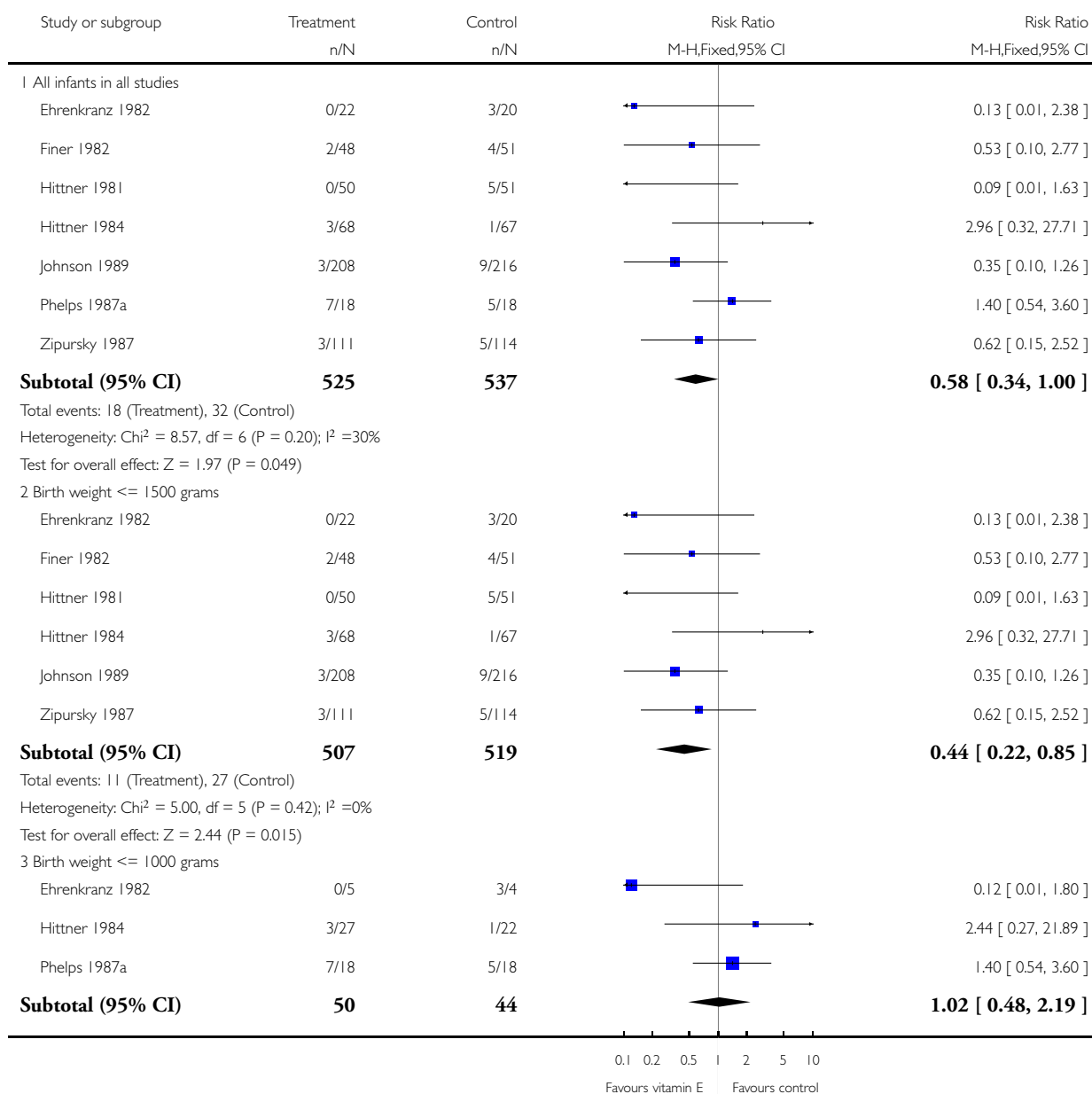


### Analysis 1.38. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 38 Severe retrolental fibroplasia/retinopathy of prematurity among very low birth weight infants examined.

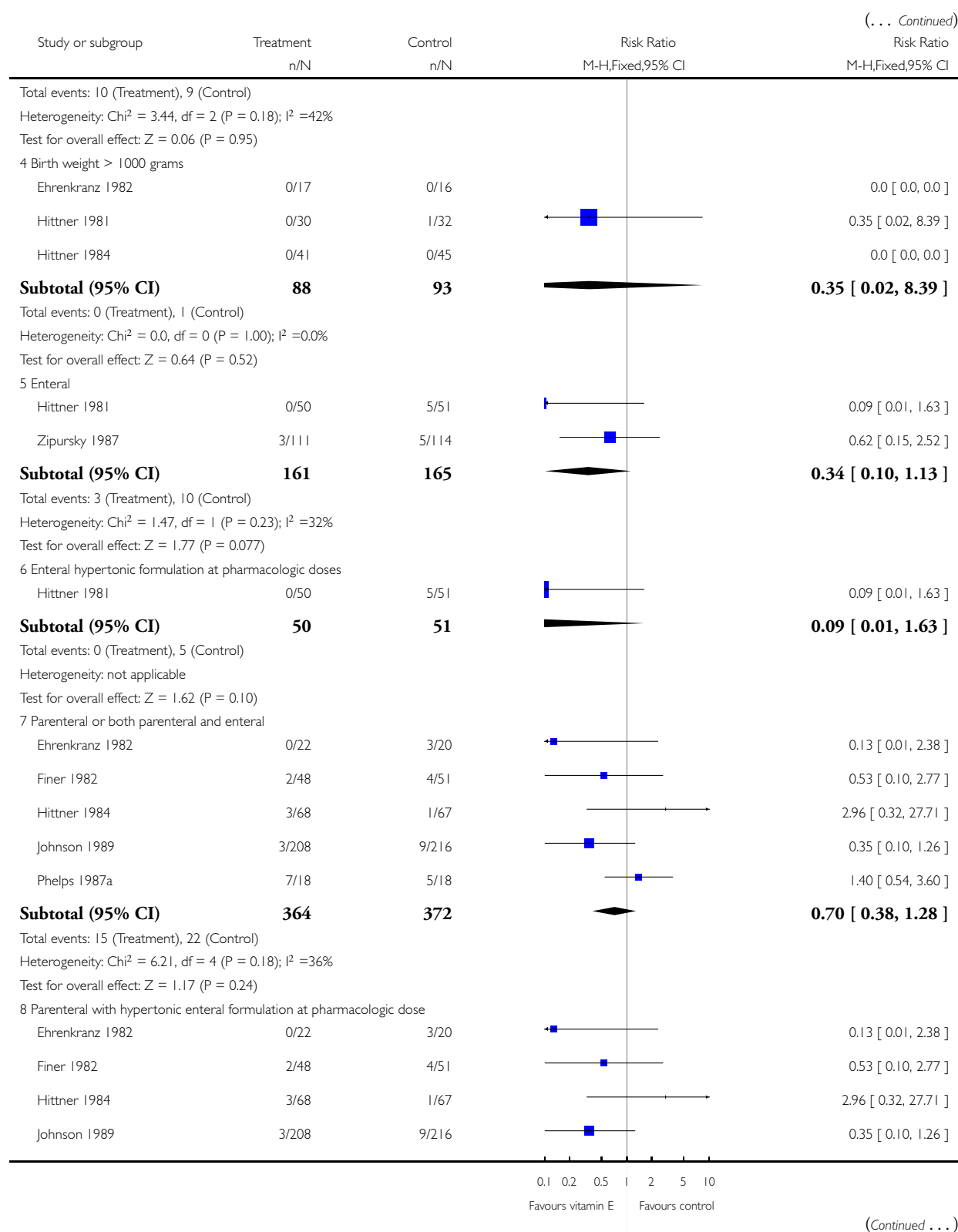
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

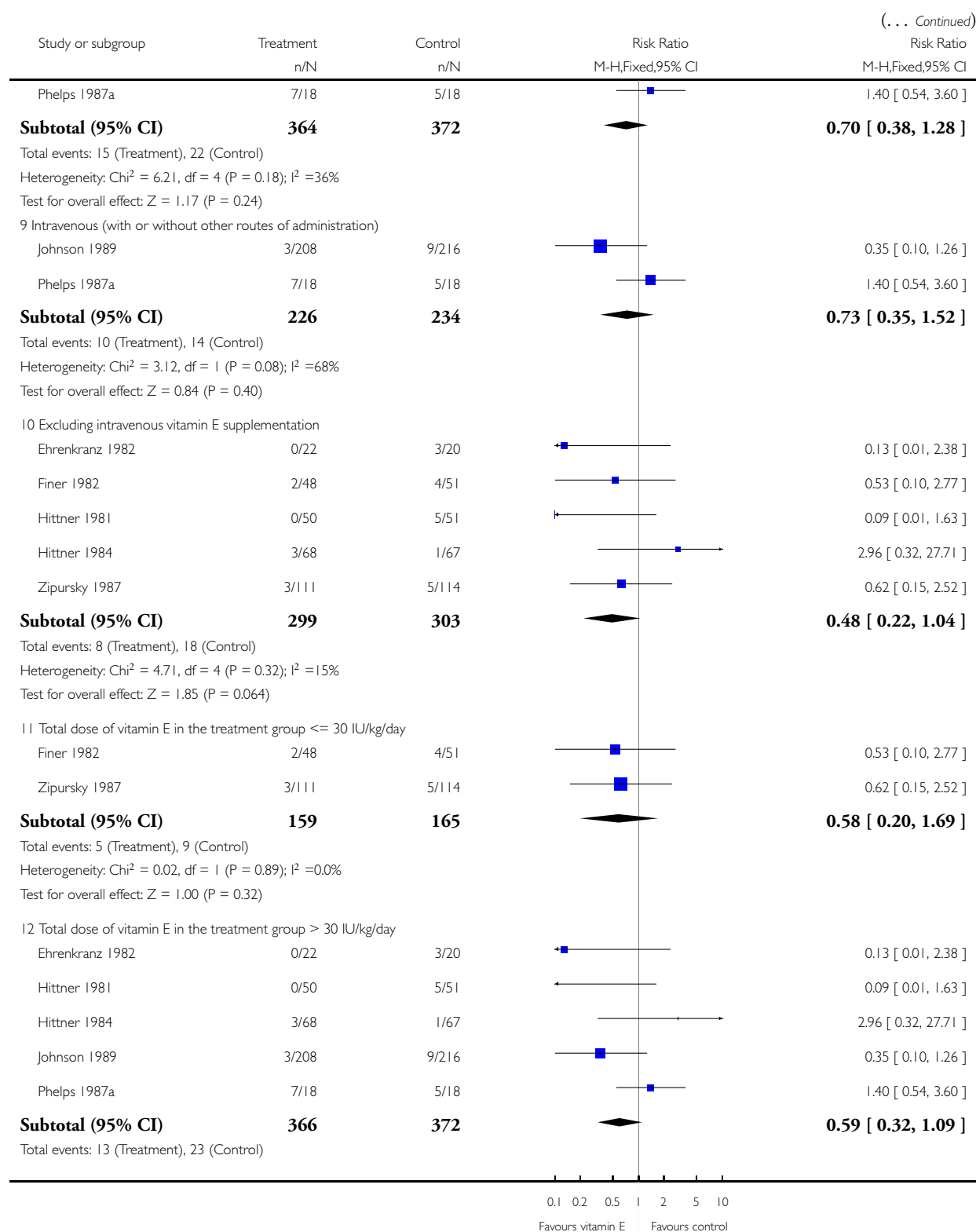
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 38 Severe retrolental fibroplasia/retinopathy of prematurity among very low birth weight infants examined

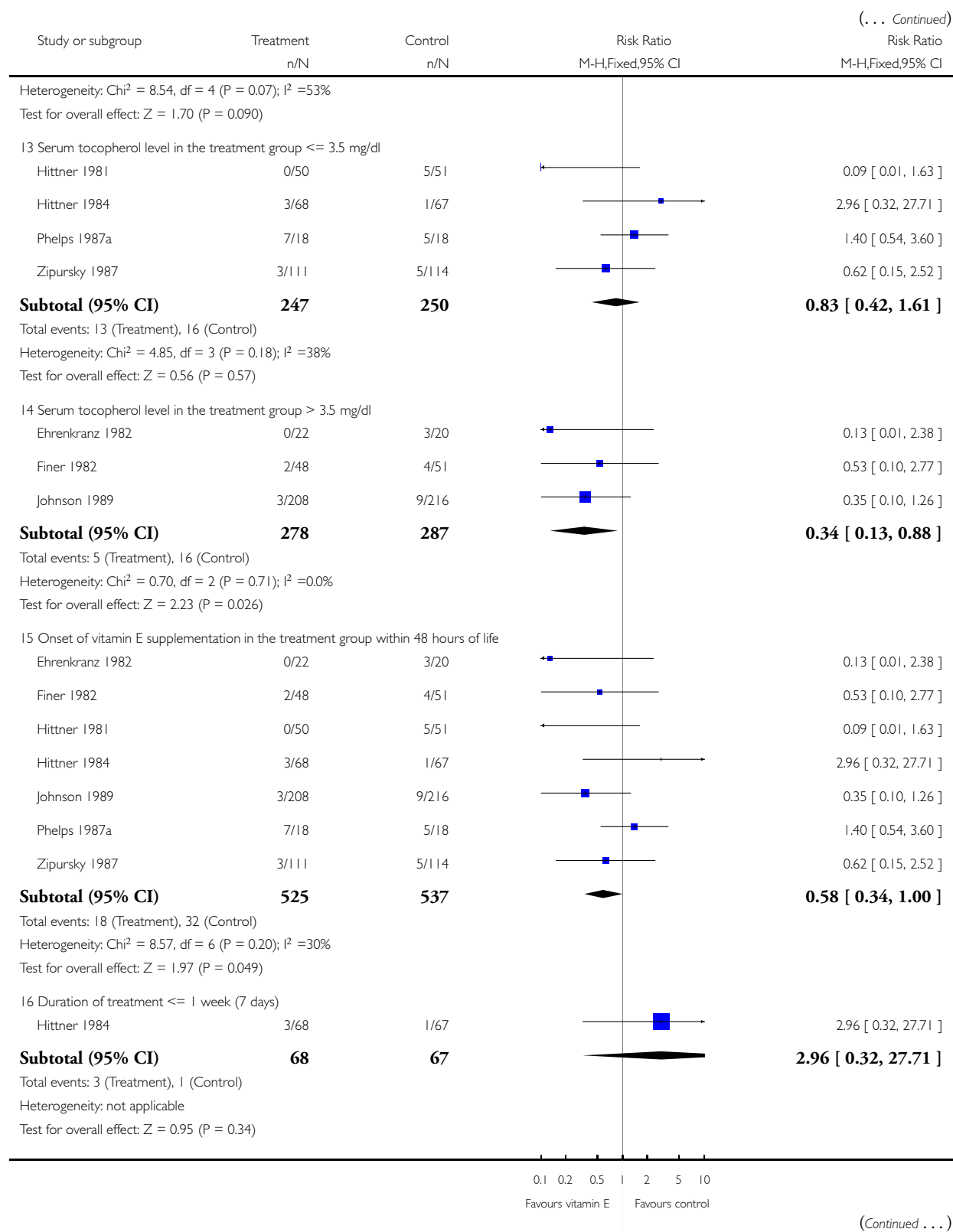


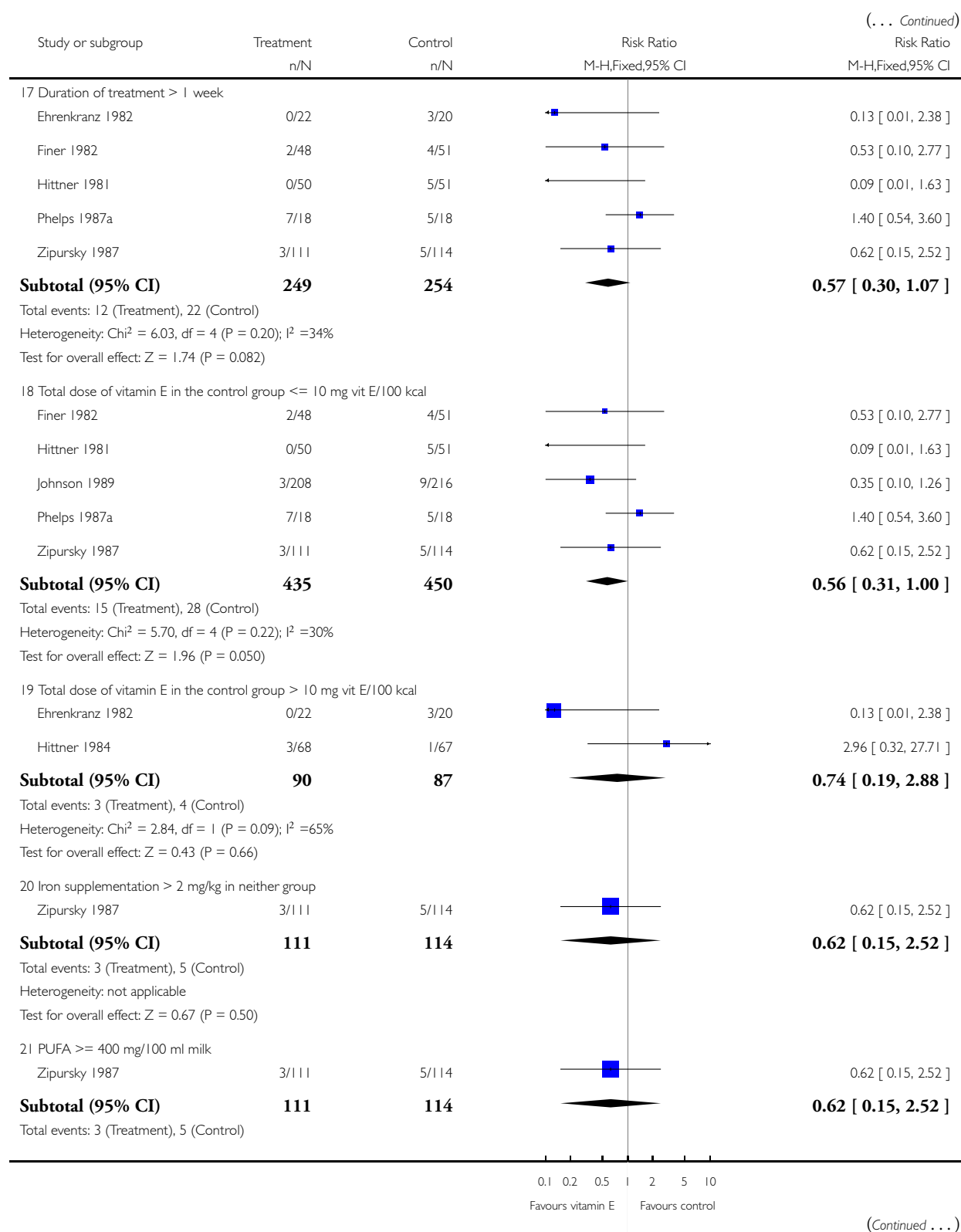
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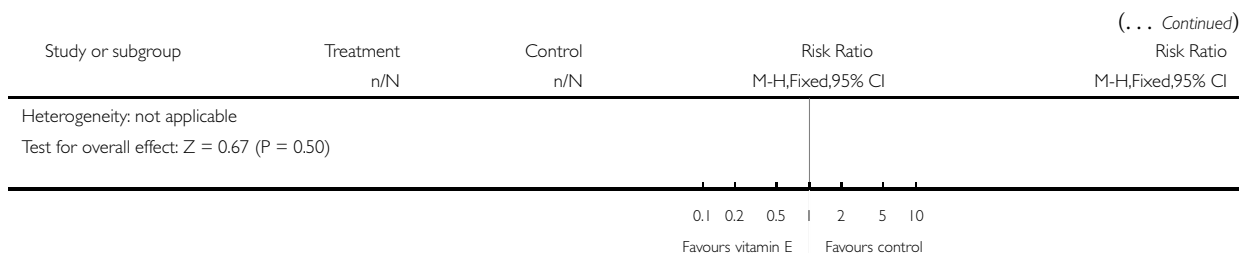


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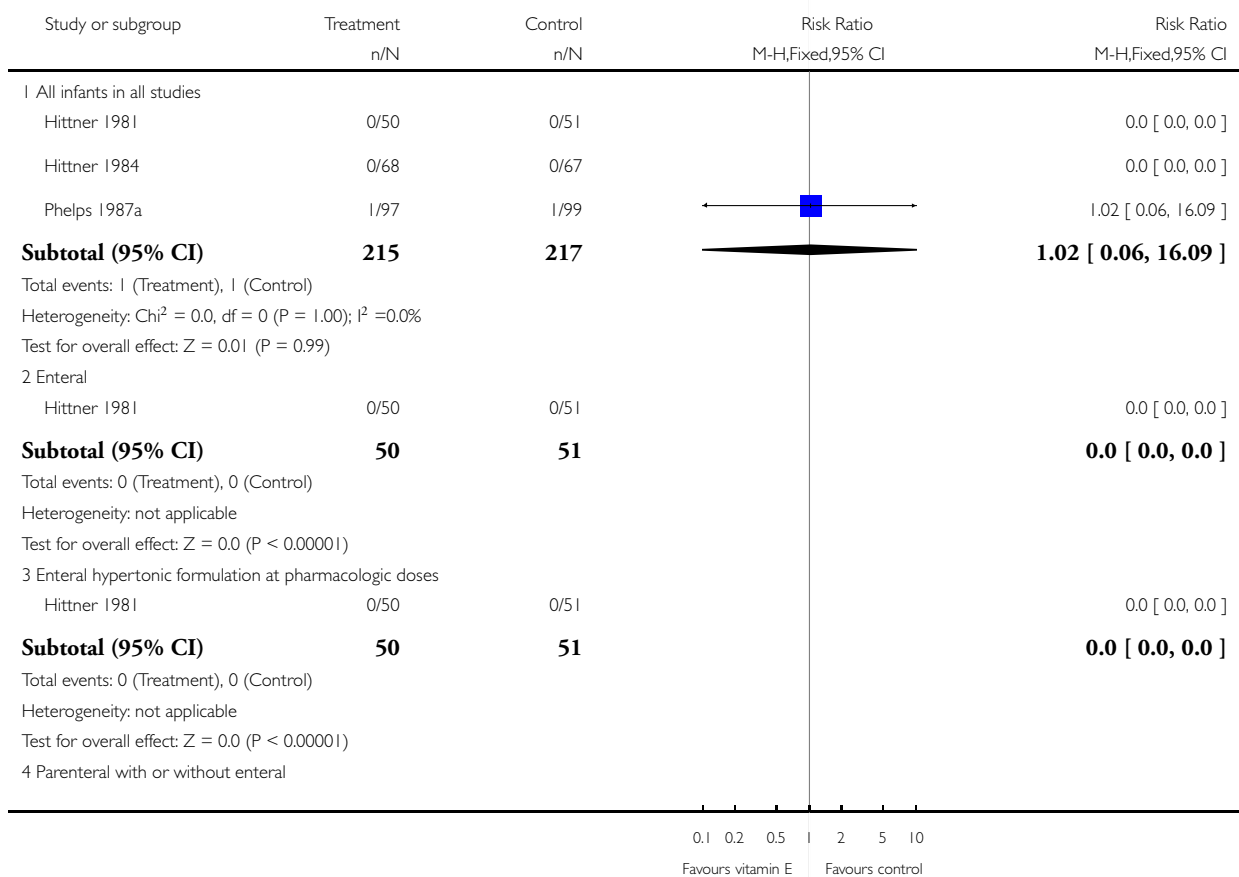


### Analysis 1.39. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 39 Retinal detachment among surviving infants.

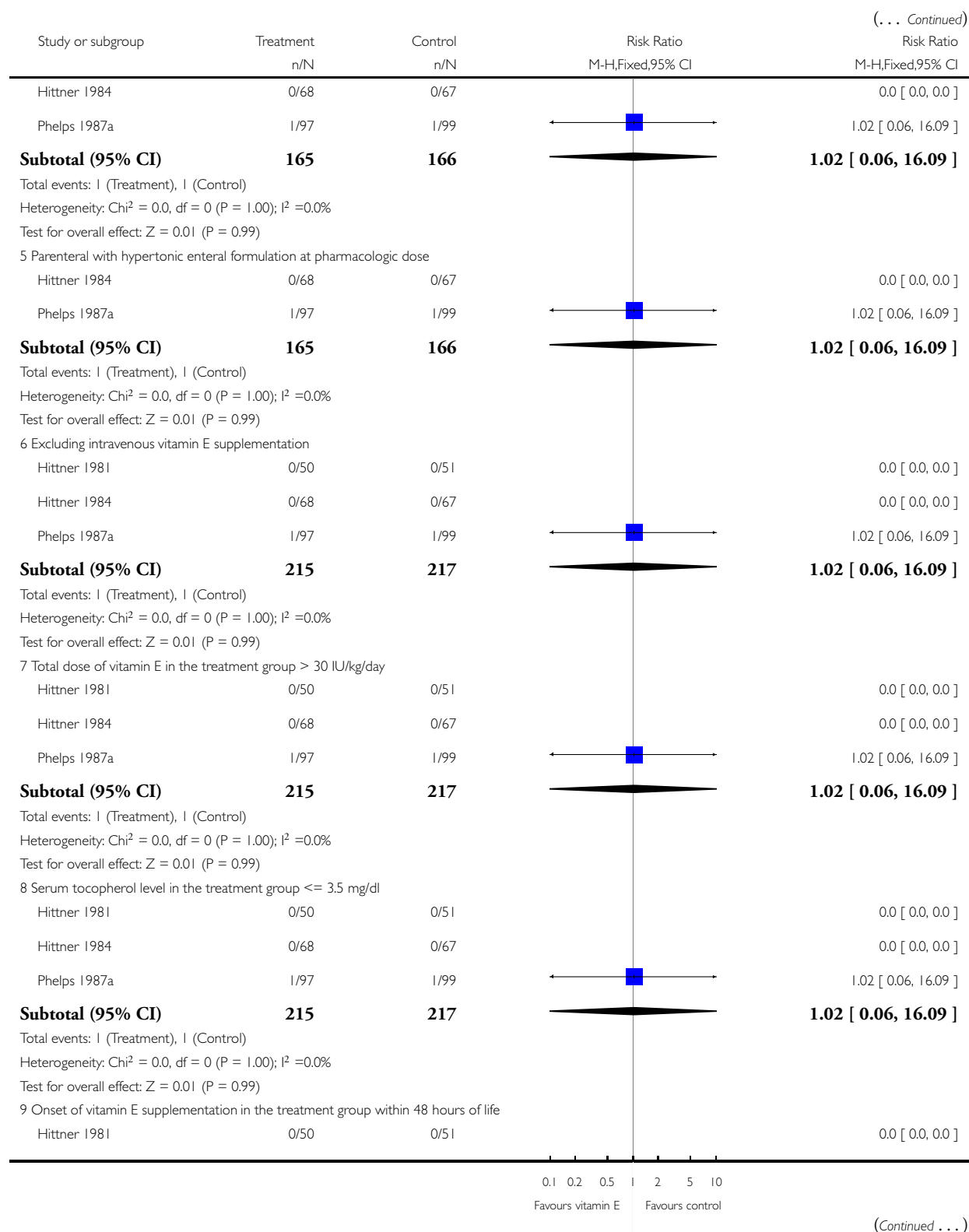
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

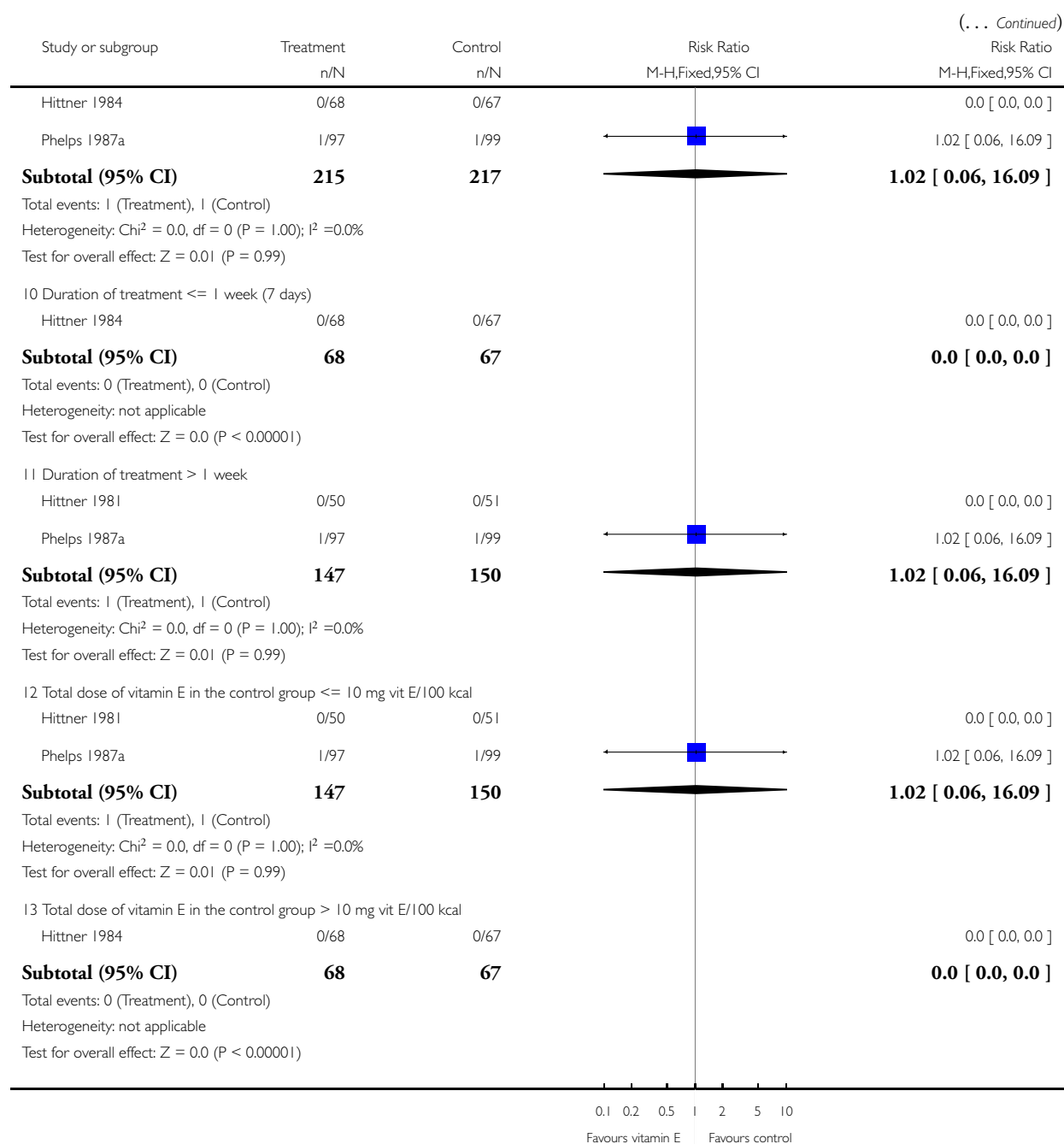
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 39 Retinal detachment among surviving infants



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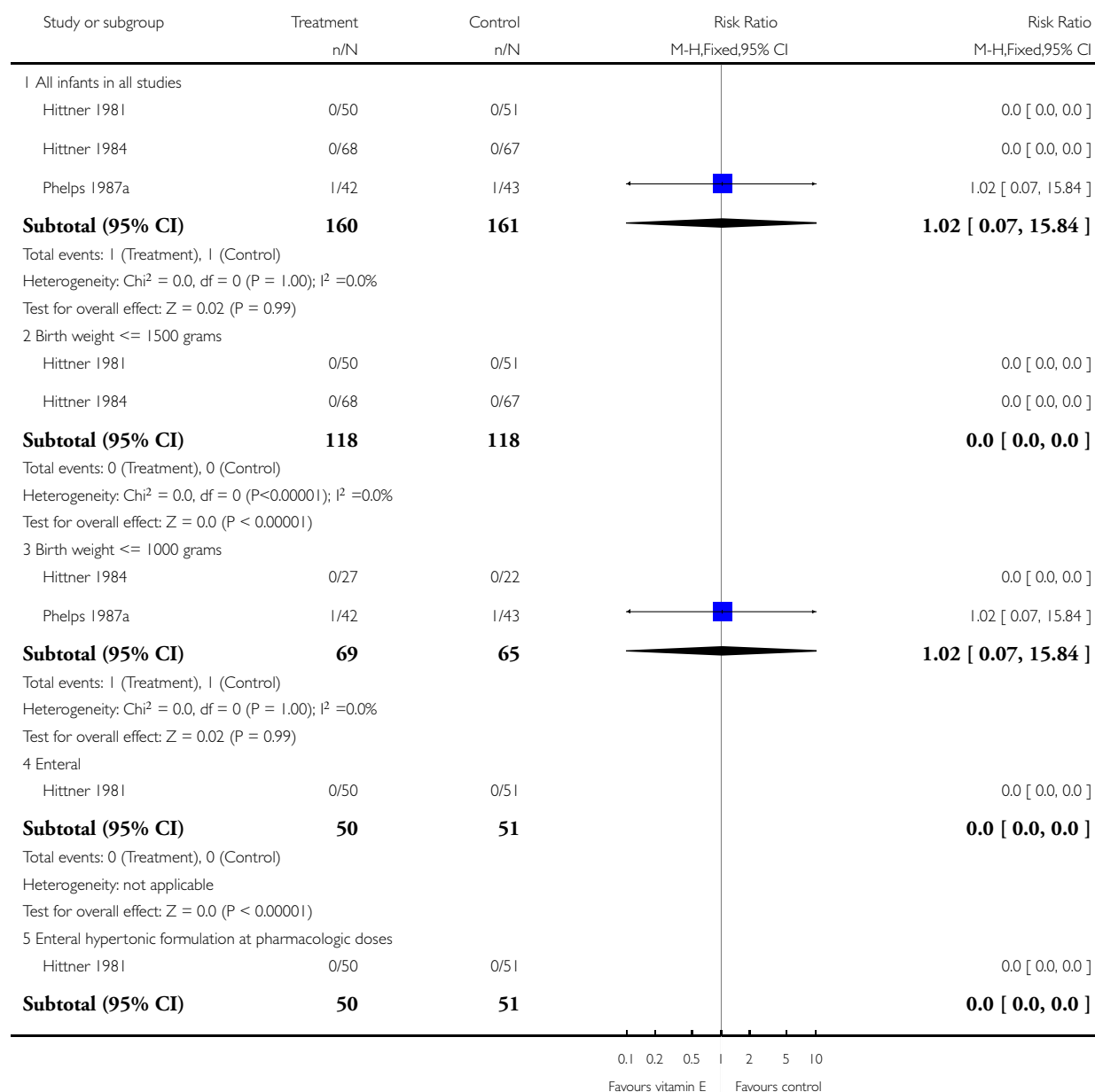


# **Analysis 1.40. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 40 Retinal detachment among surviving very low birth weight infants.**

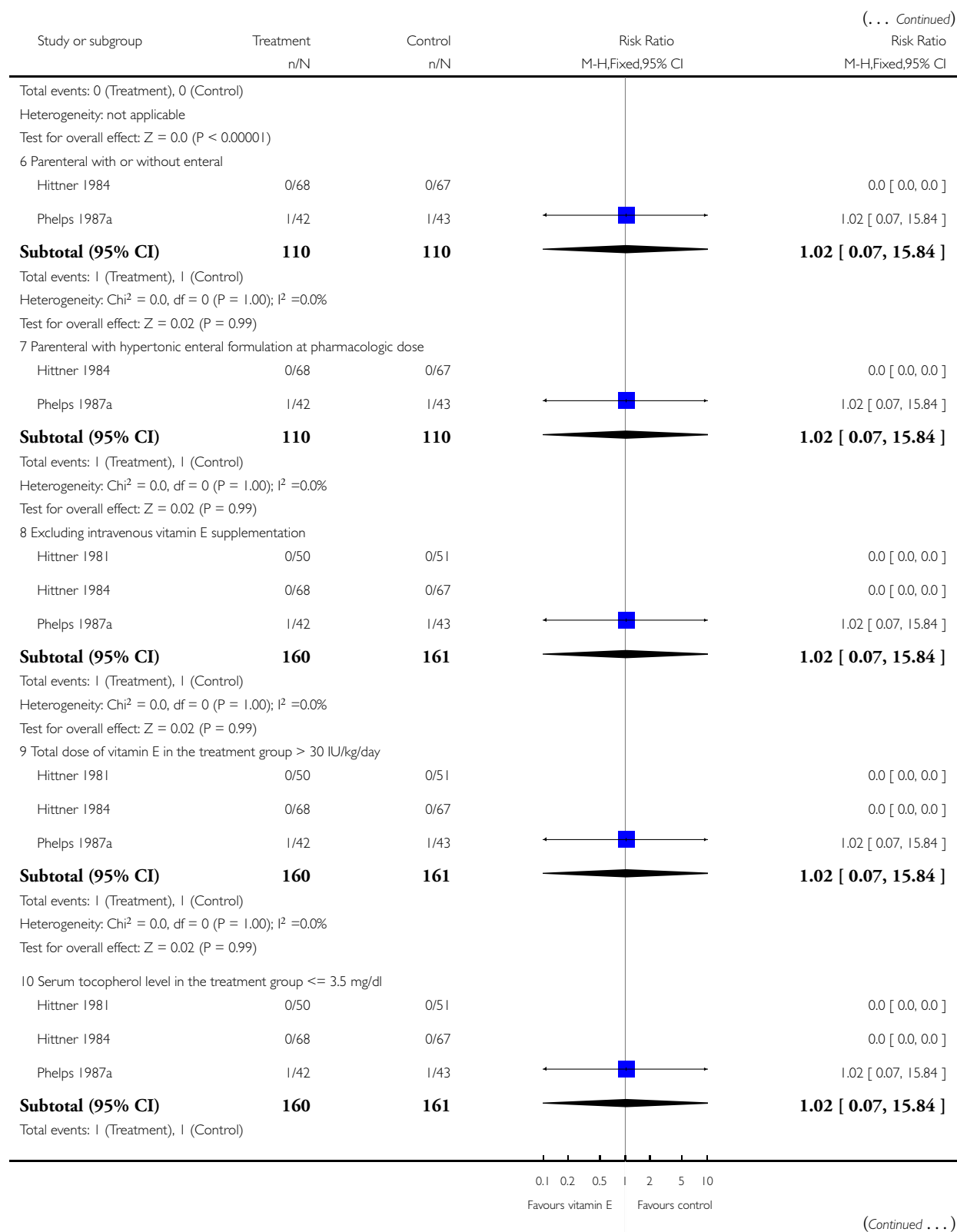
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

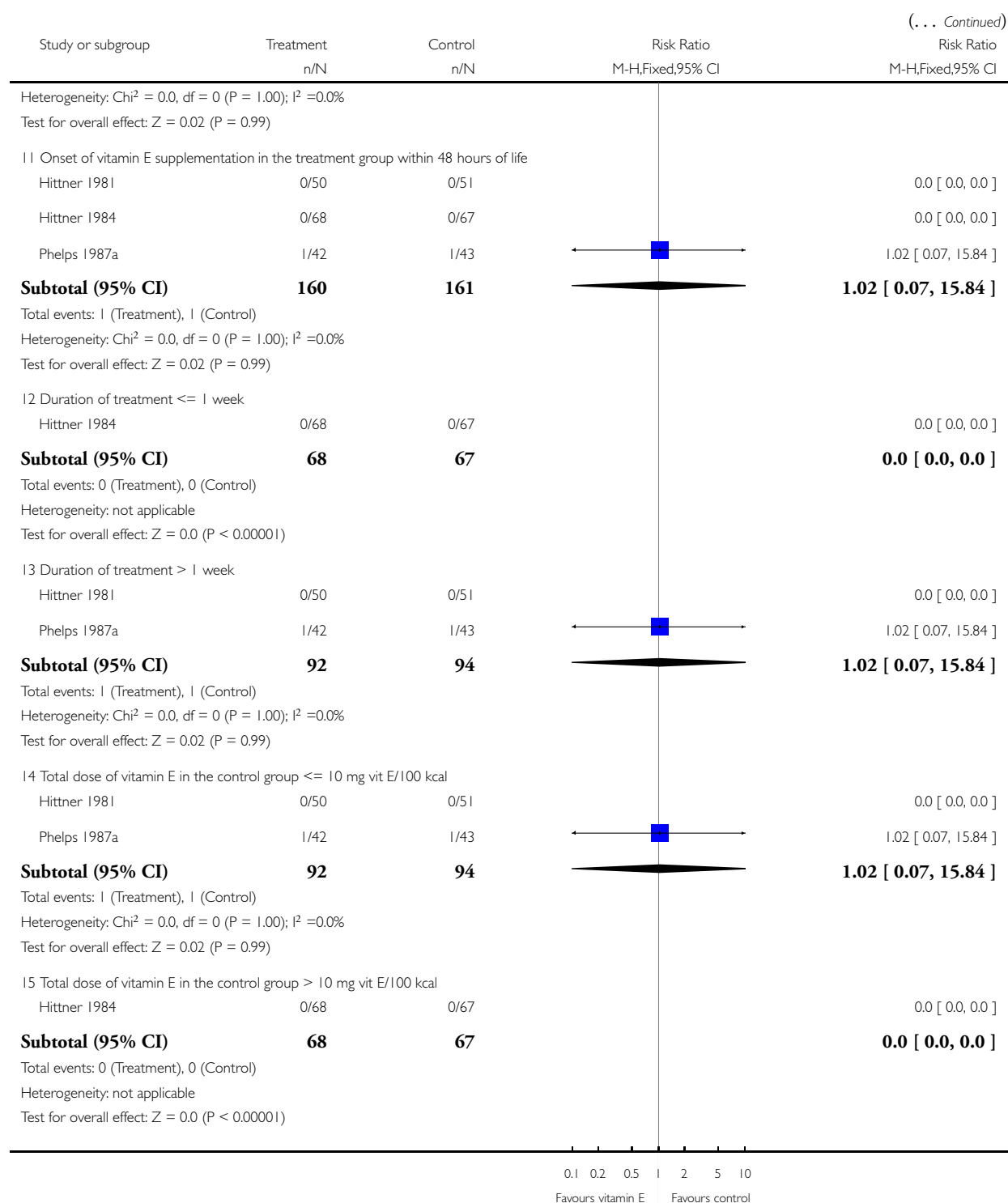
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 40 Retinal detachment among surviving very low birth weight infants



(Continued . . .)



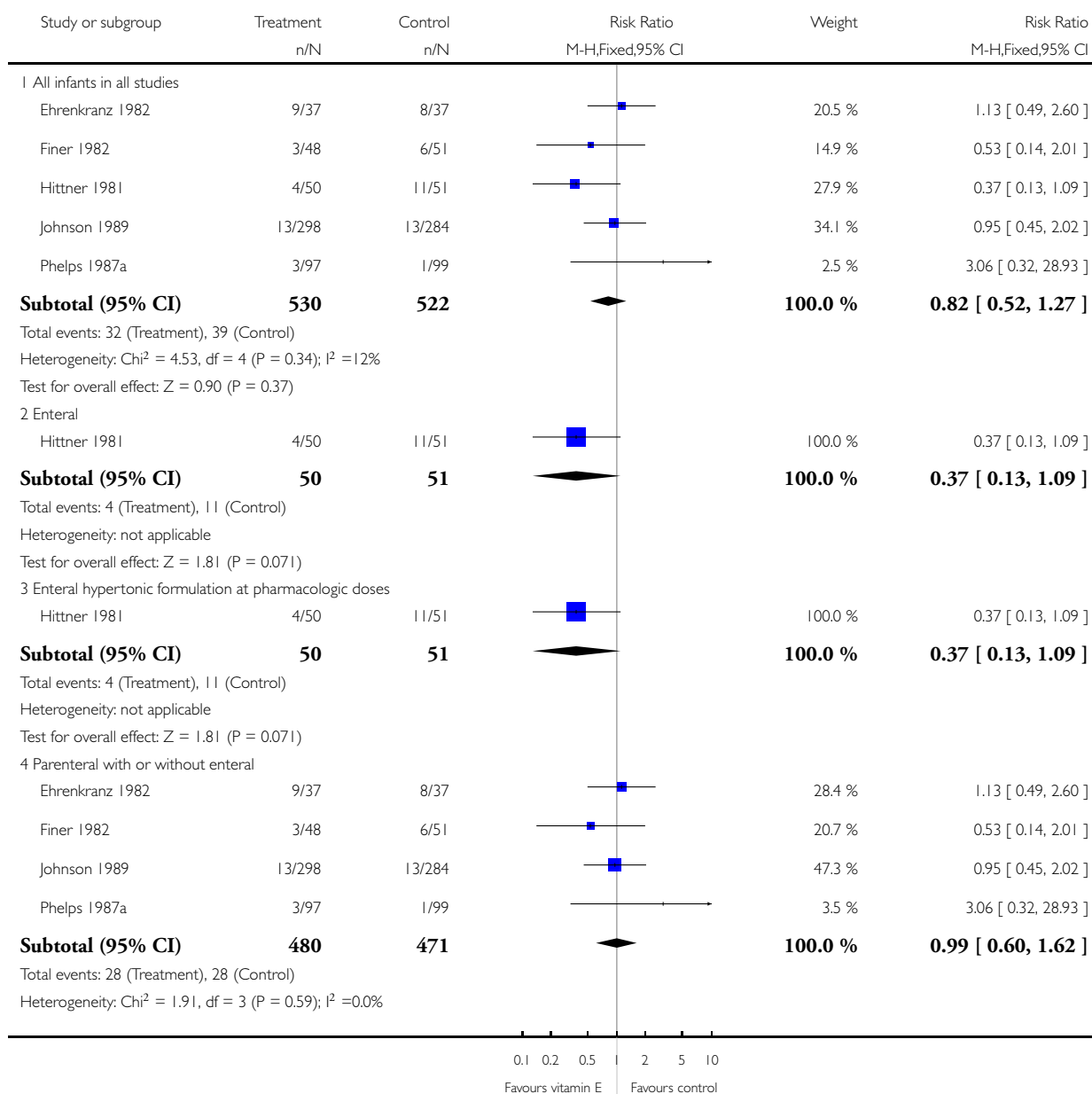


# **Analysis 1.41. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 41 Cicatricial retrolental fibroplasia, any stage, among patients examined after discharge.**

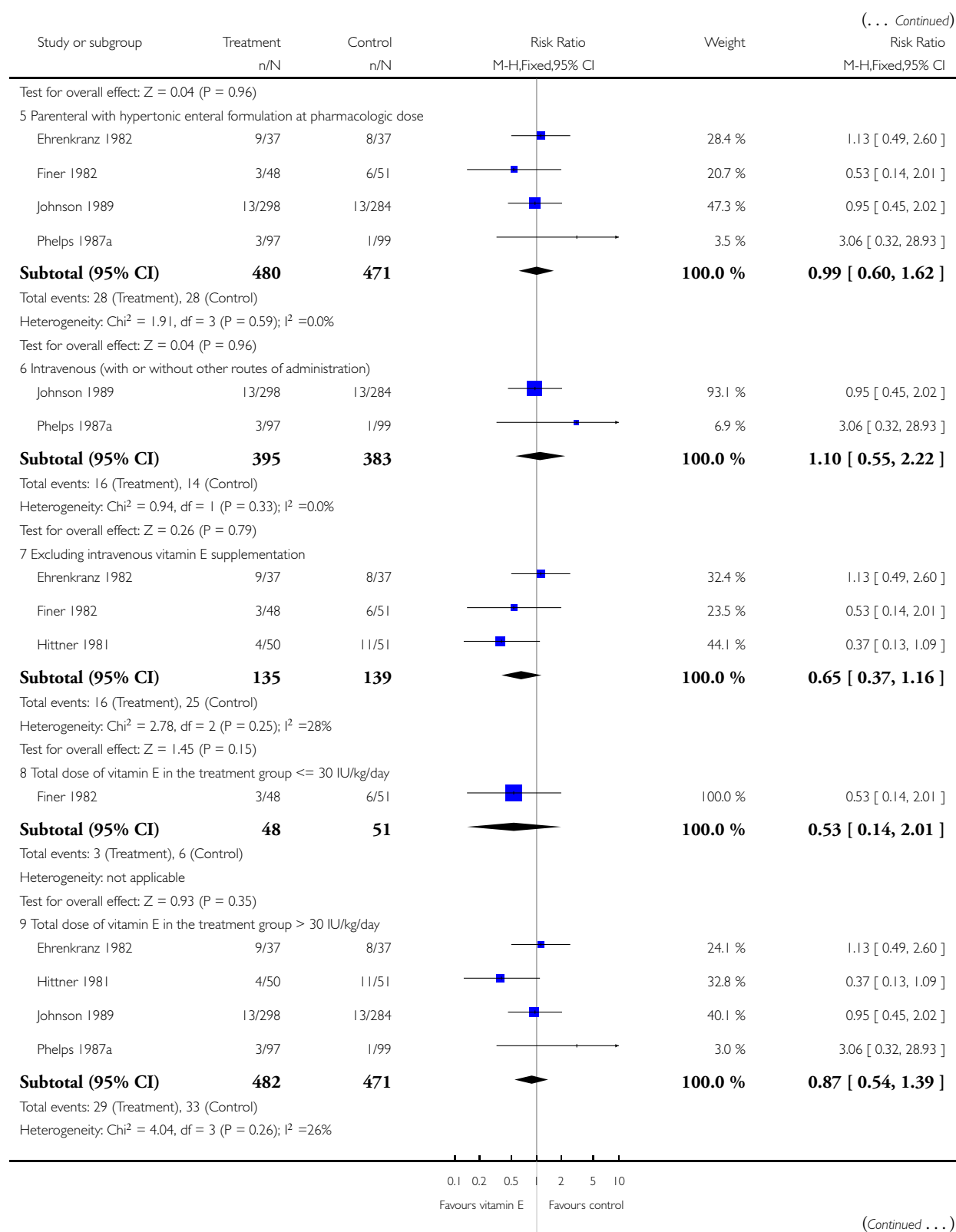
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

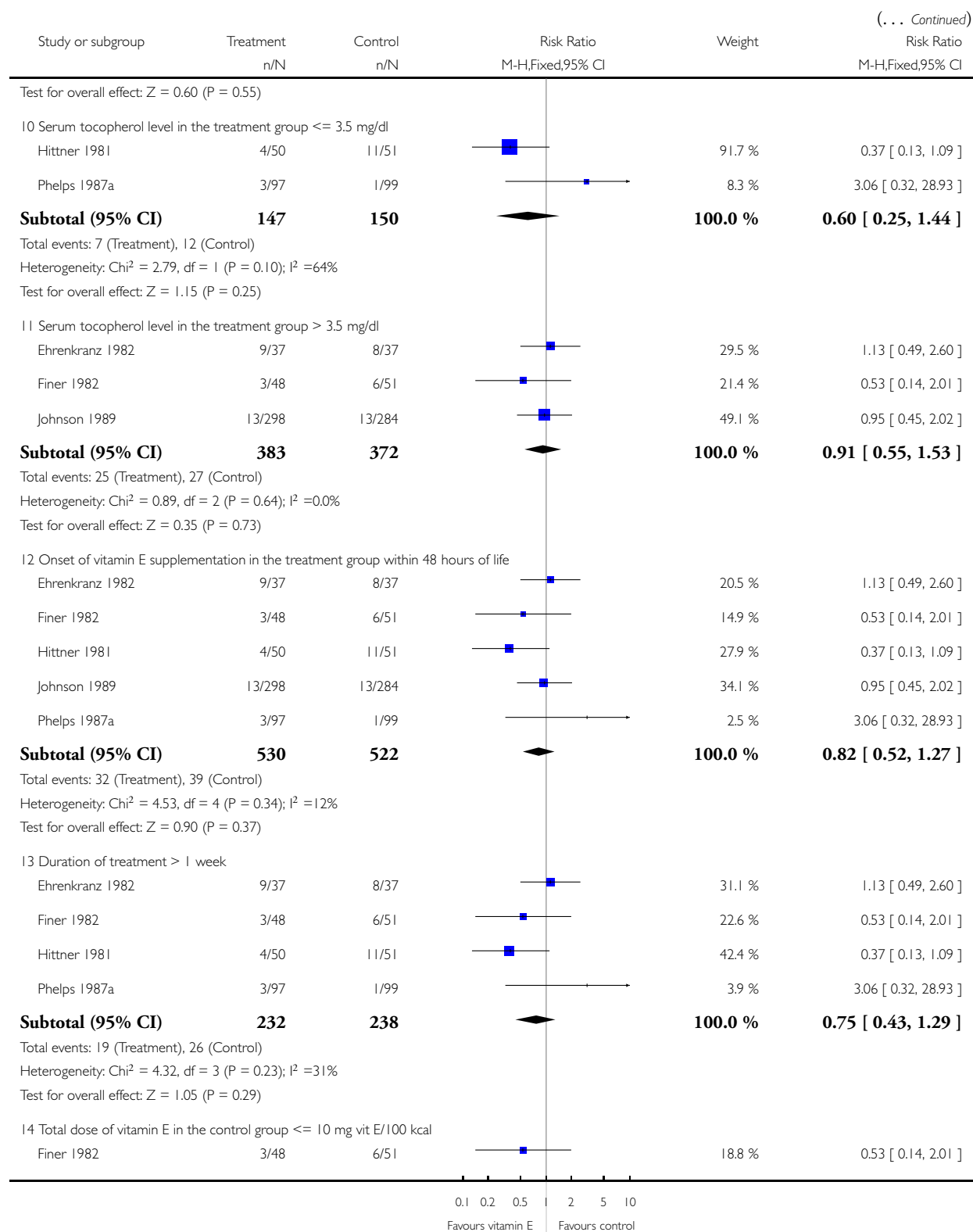
Outcome: 41 Cicatricial retrolental fibroplasia, any stage, among patients examined after discharge

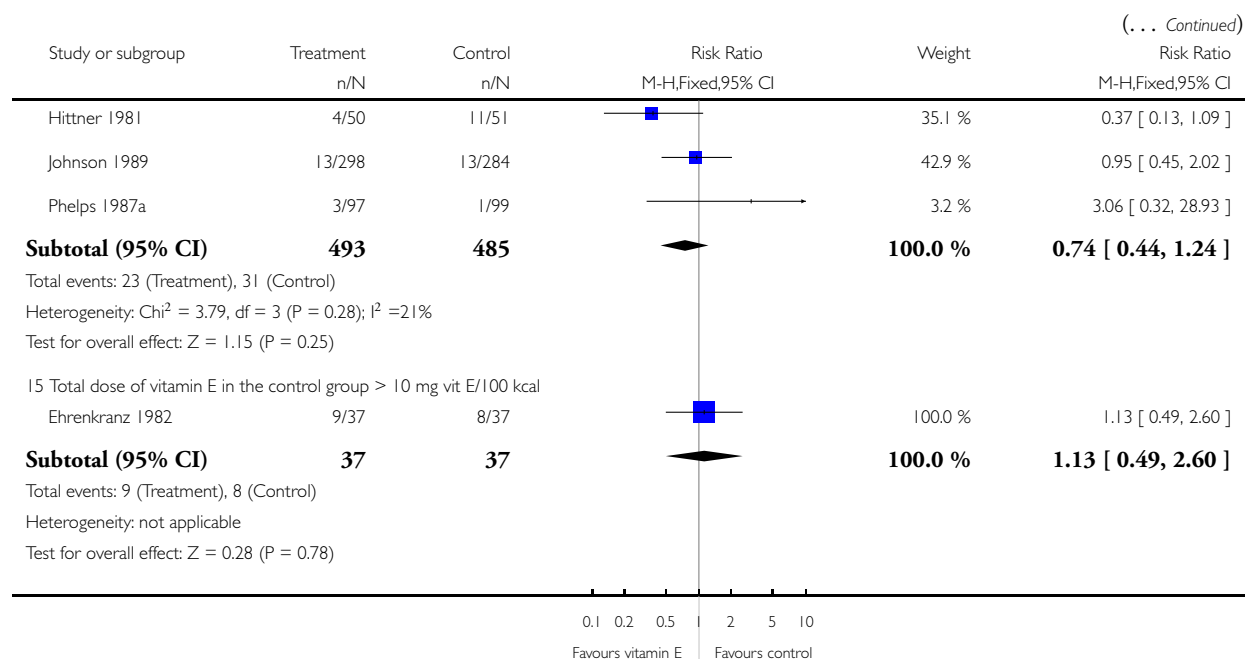


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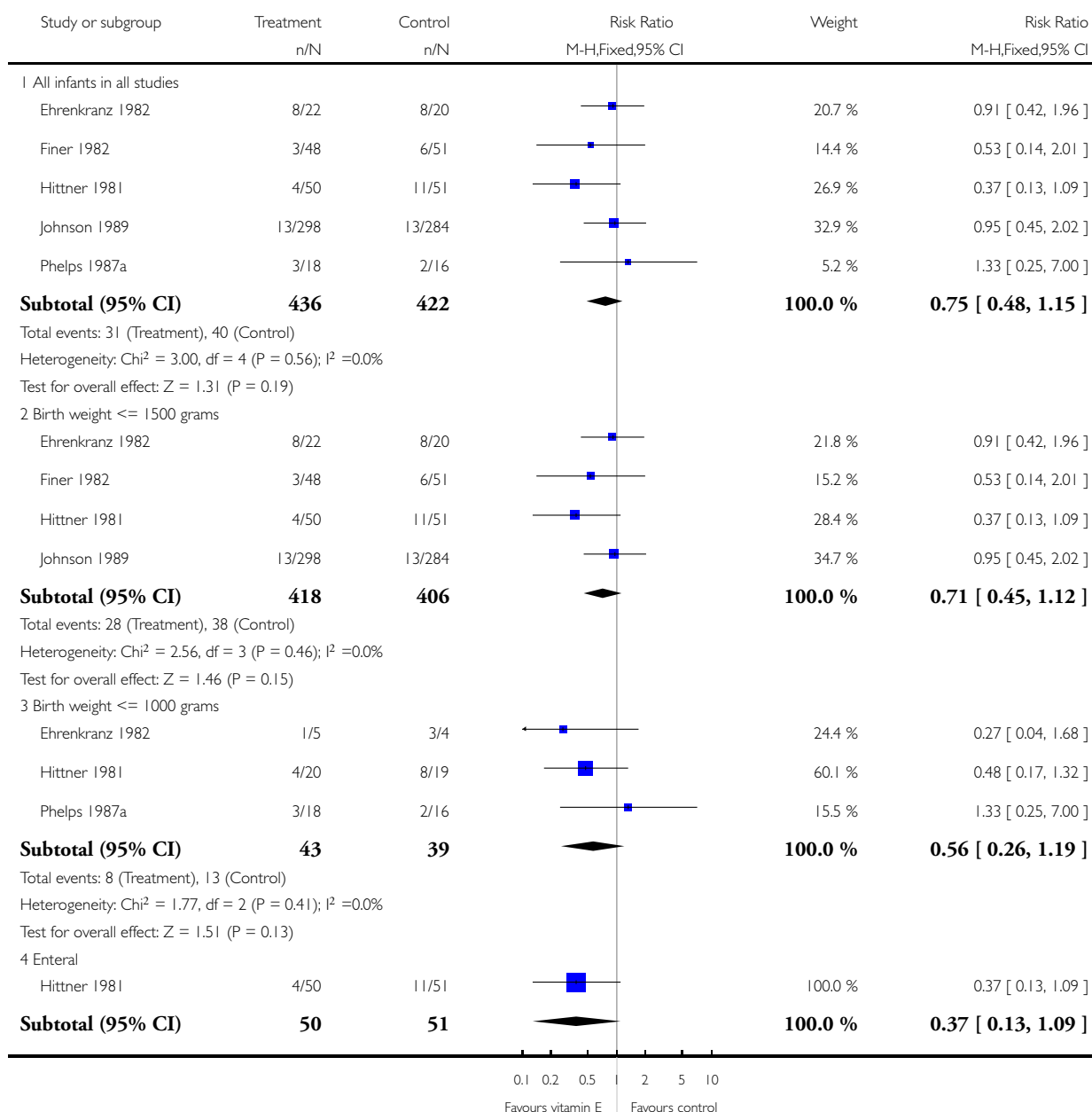


# **Analysis 1.42. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 42 Cicatricial retrolental fibroplasia, any stage, among very low birth weight infants examined after discharge.**

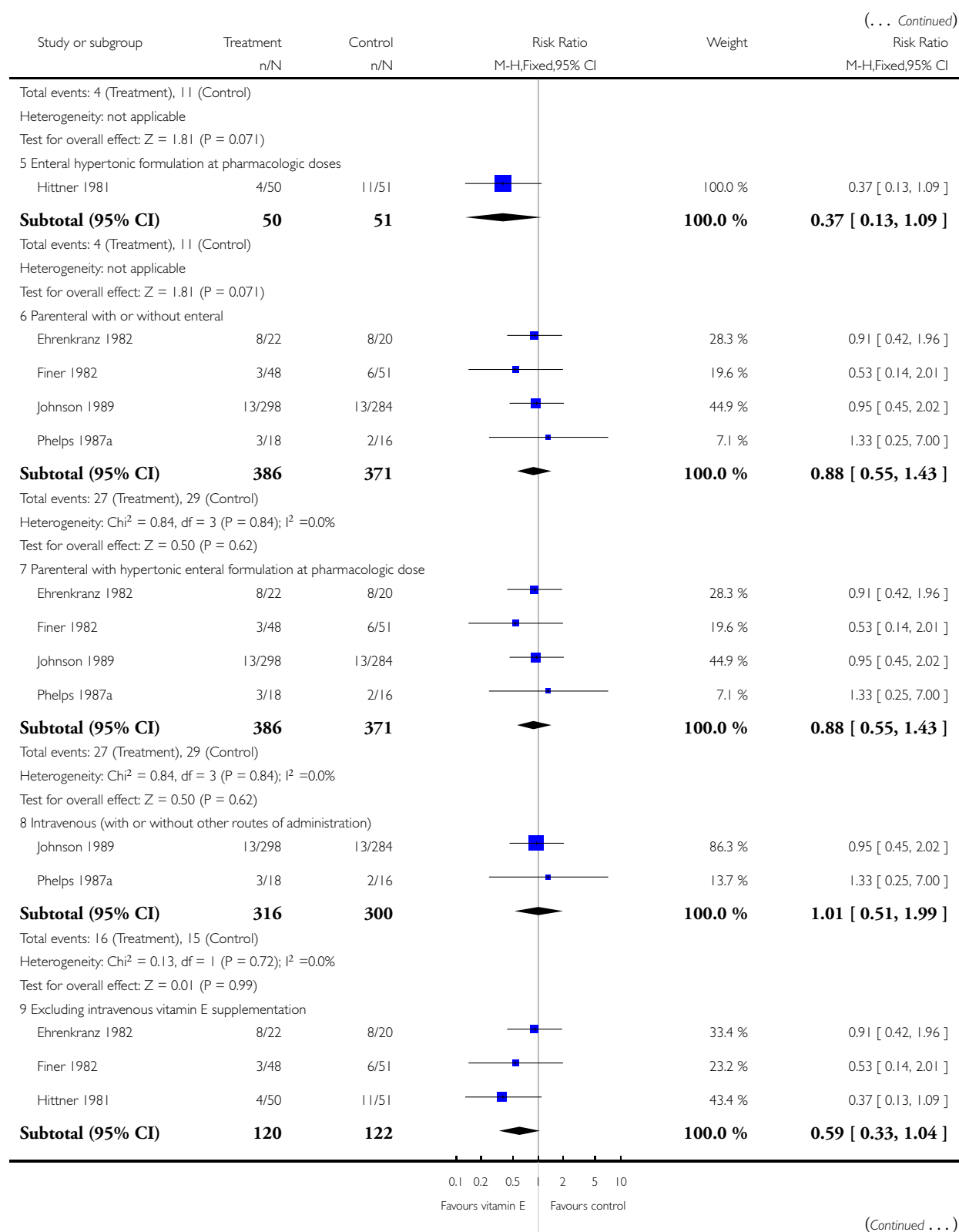
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

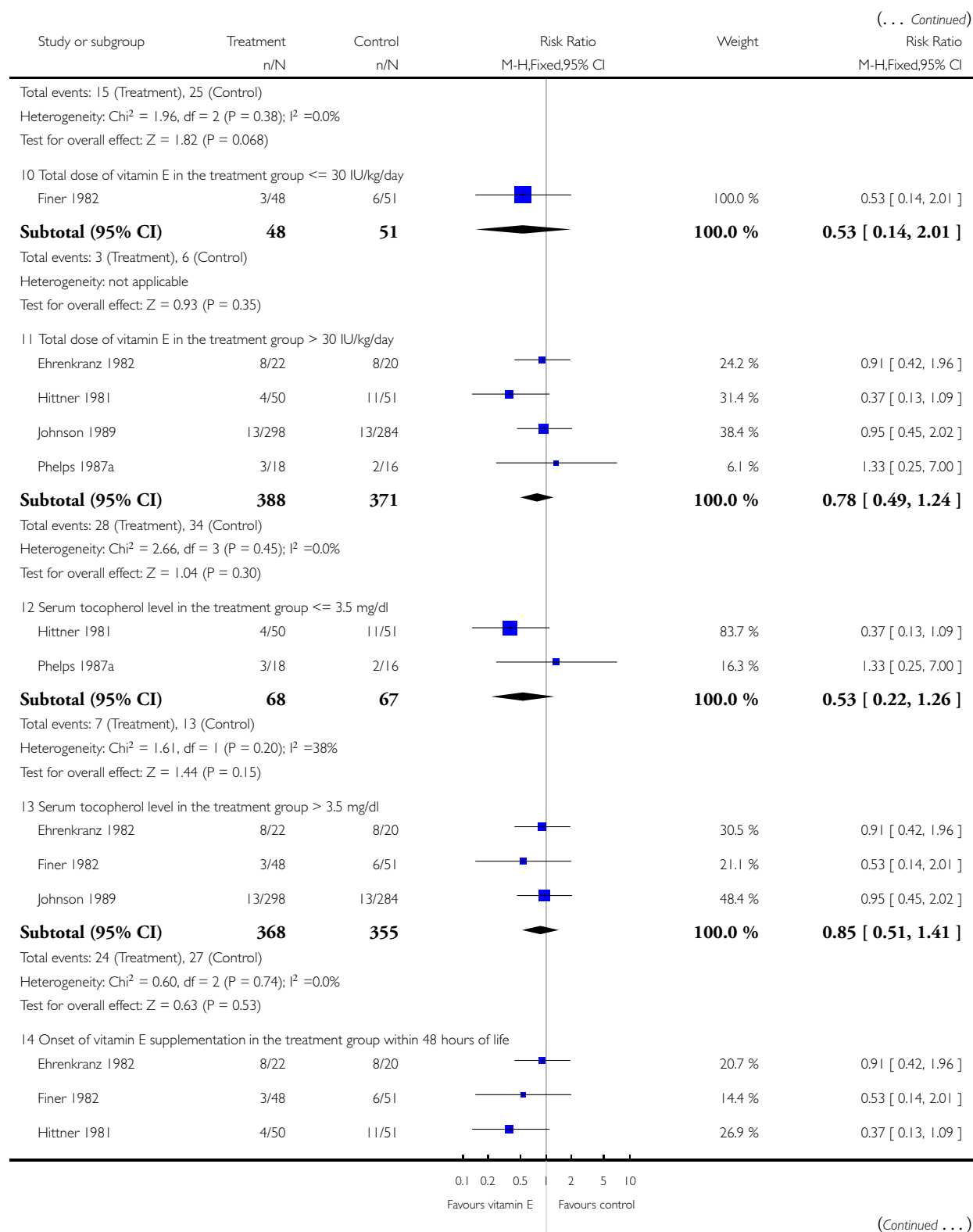
Comparison: 1 Vitamin E versus placebo or no vitamin E

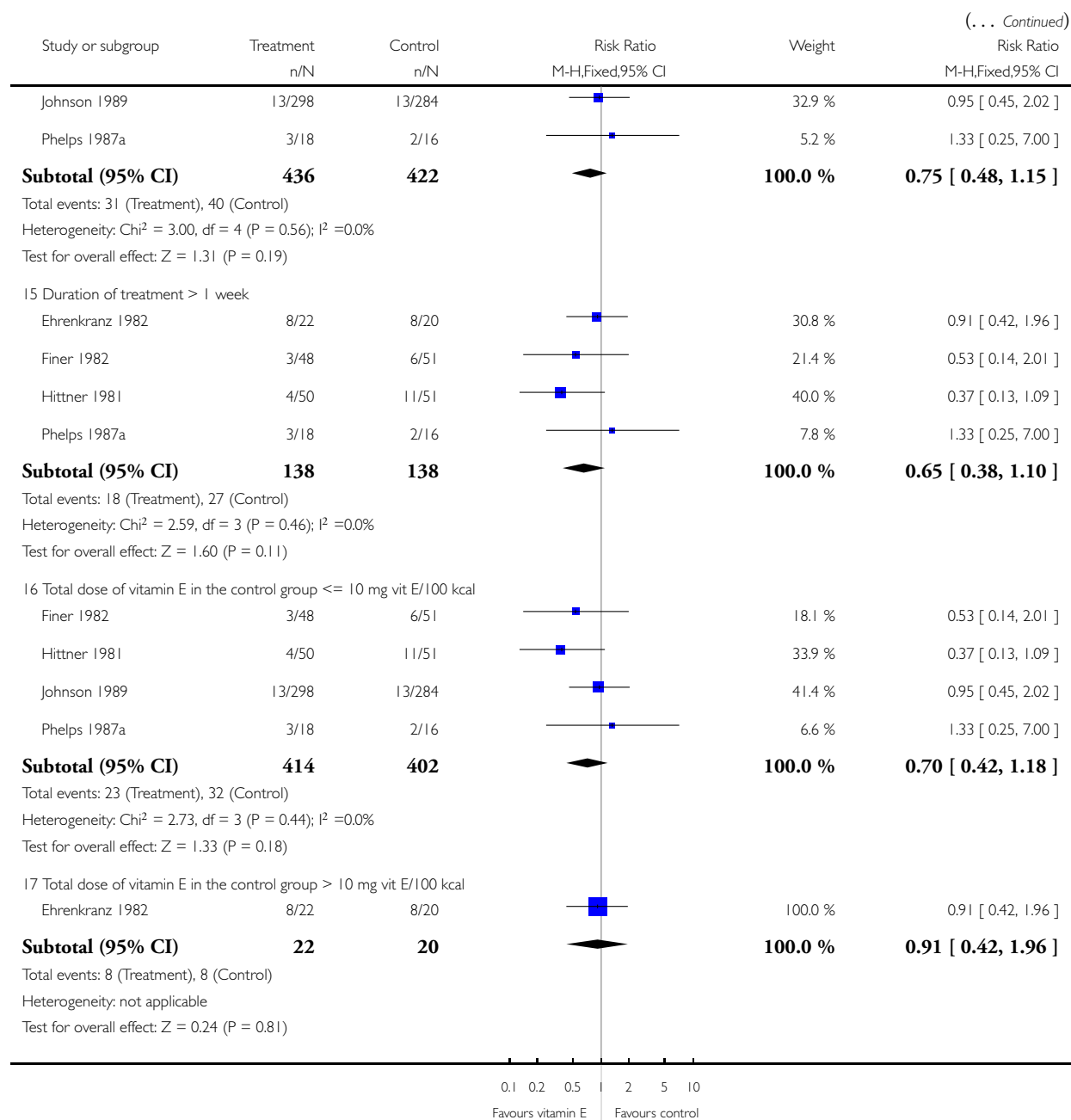
Outcome: 42 Cicatricial retrolental fibroplasia, any stage, among very low birth weight infants examined after discharge



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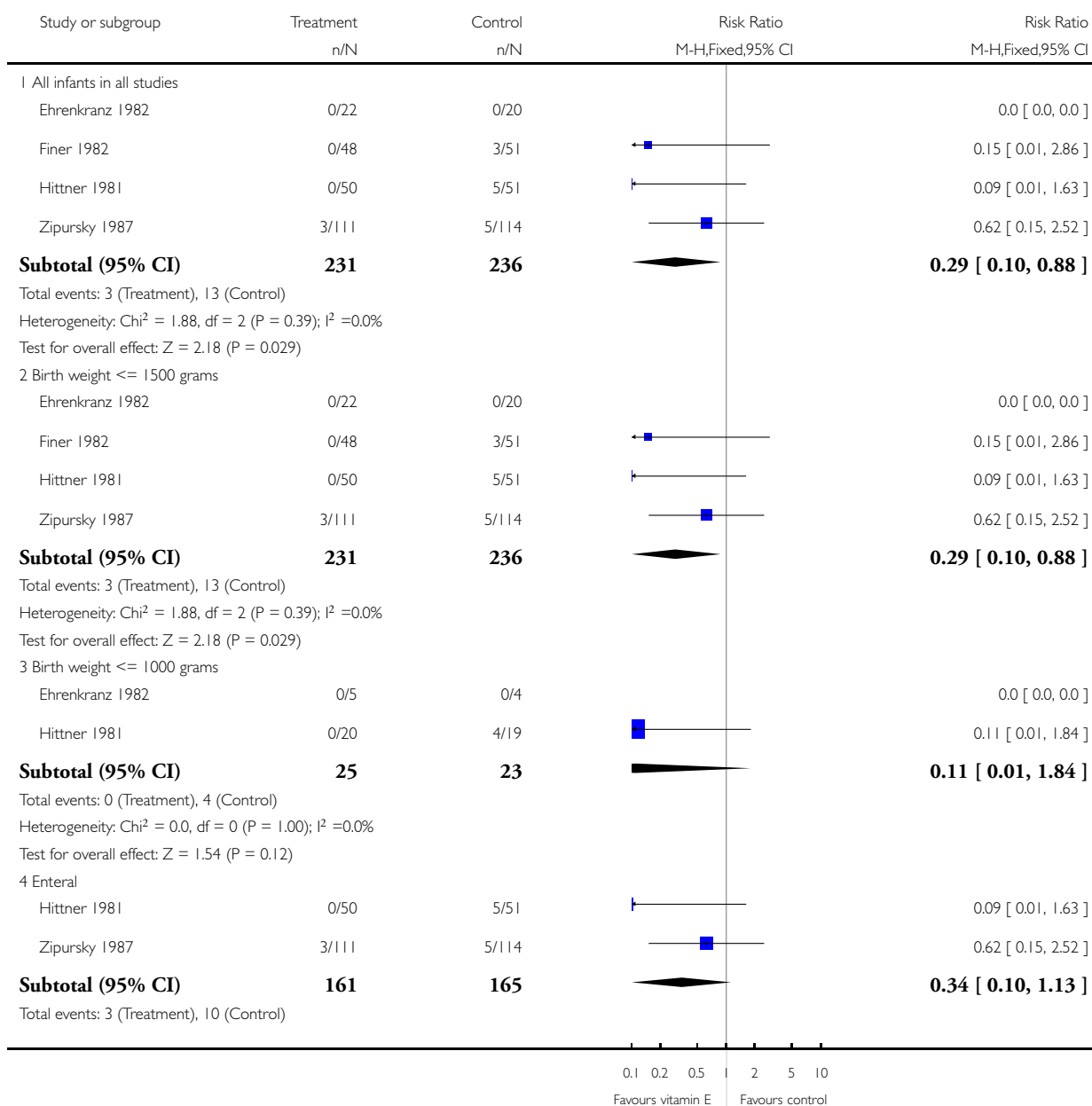


### Analysis 1.43. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 43 Blindness from retrolental fibroplasia among very low birth weight infants examined.

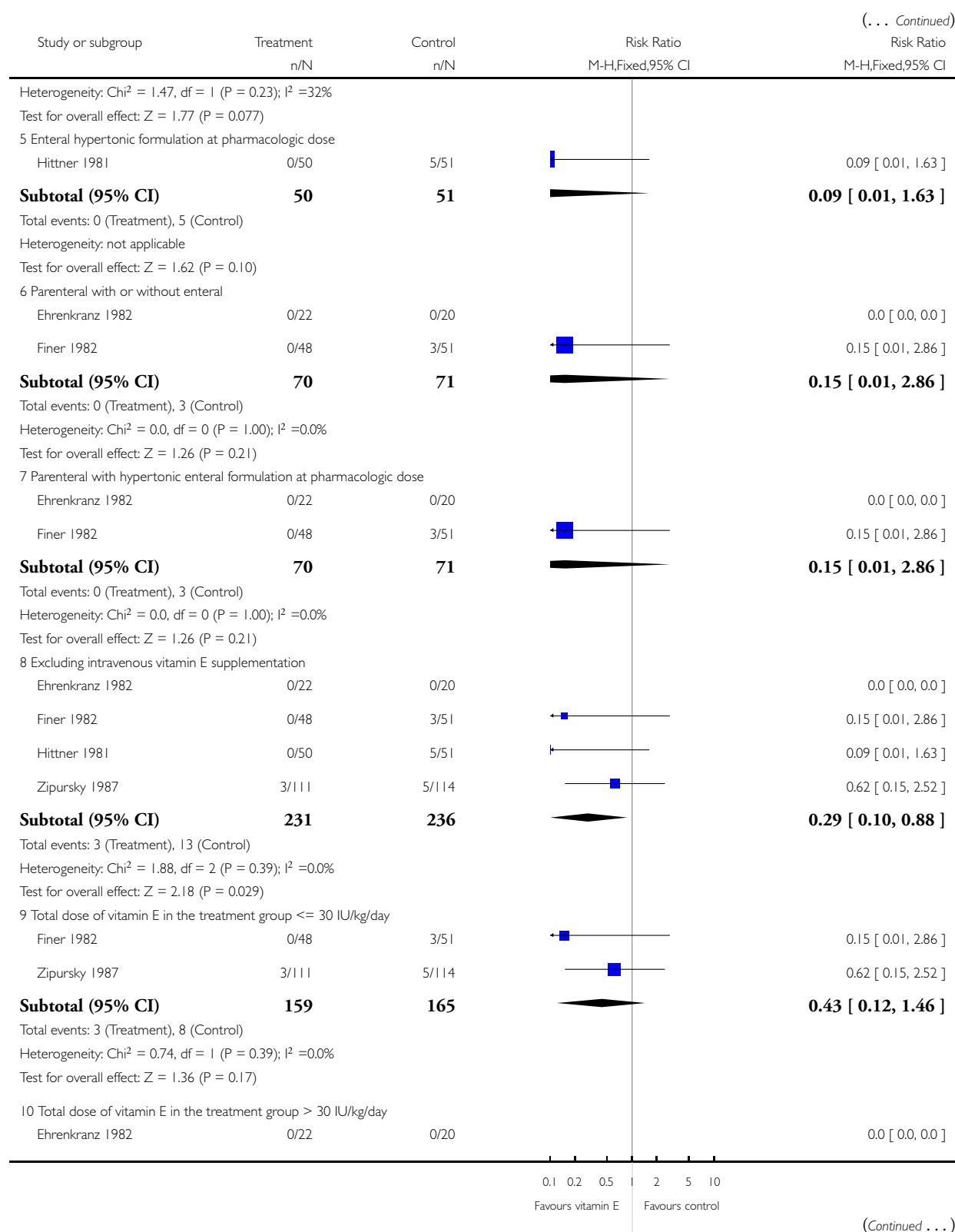
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

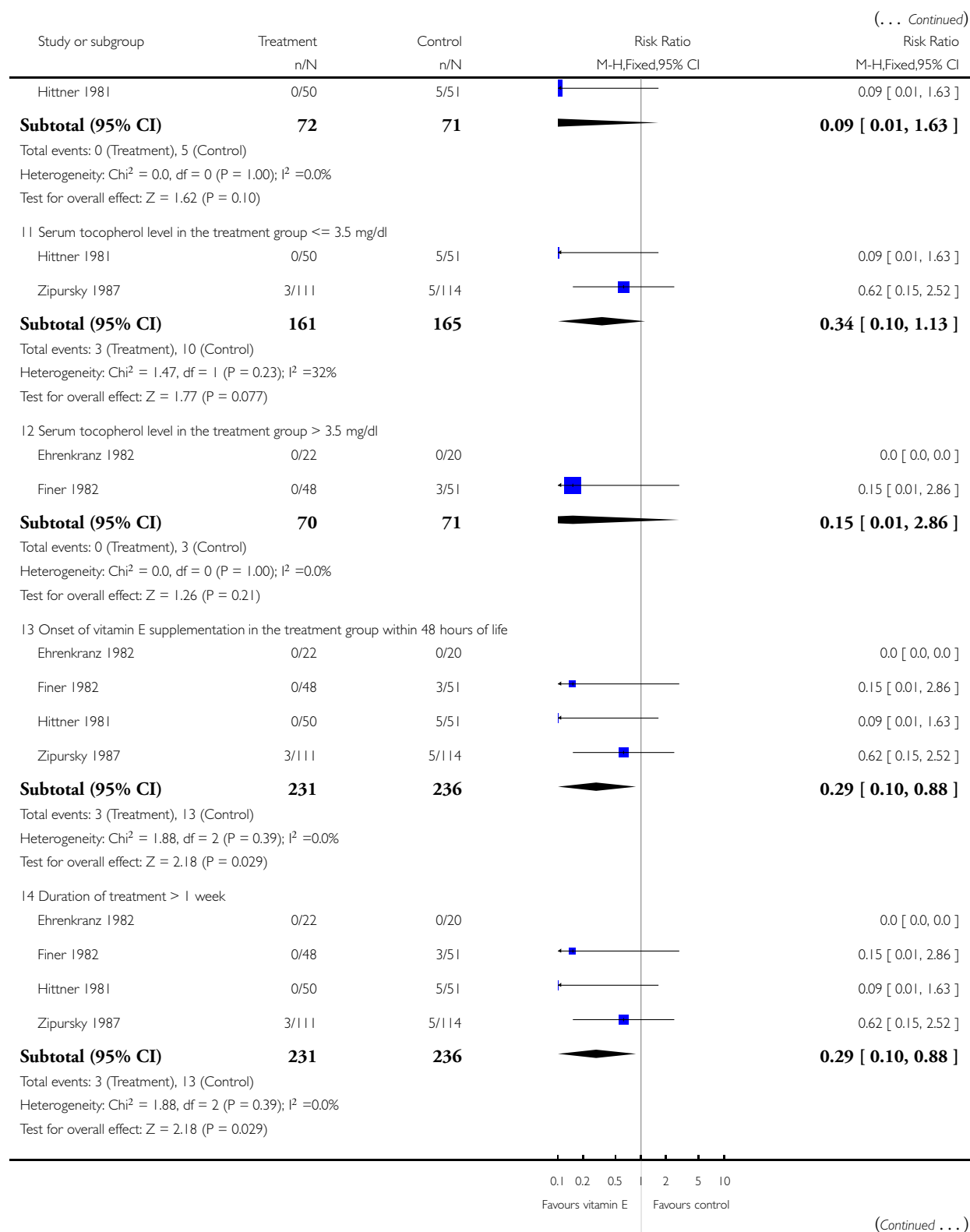
Outcome: 43 Blindness from retrolental fibroplasia among very low birth weight infants examined

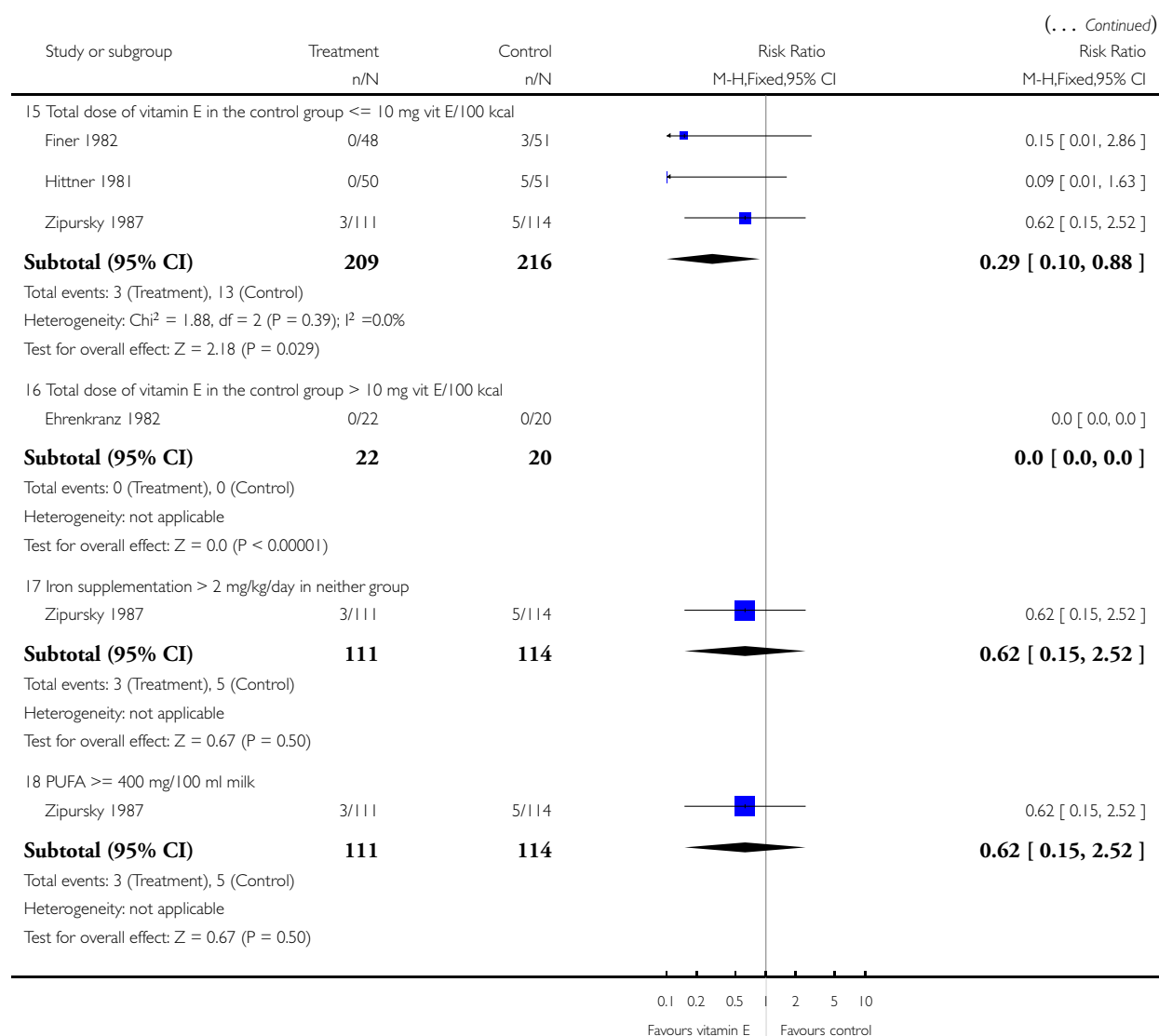


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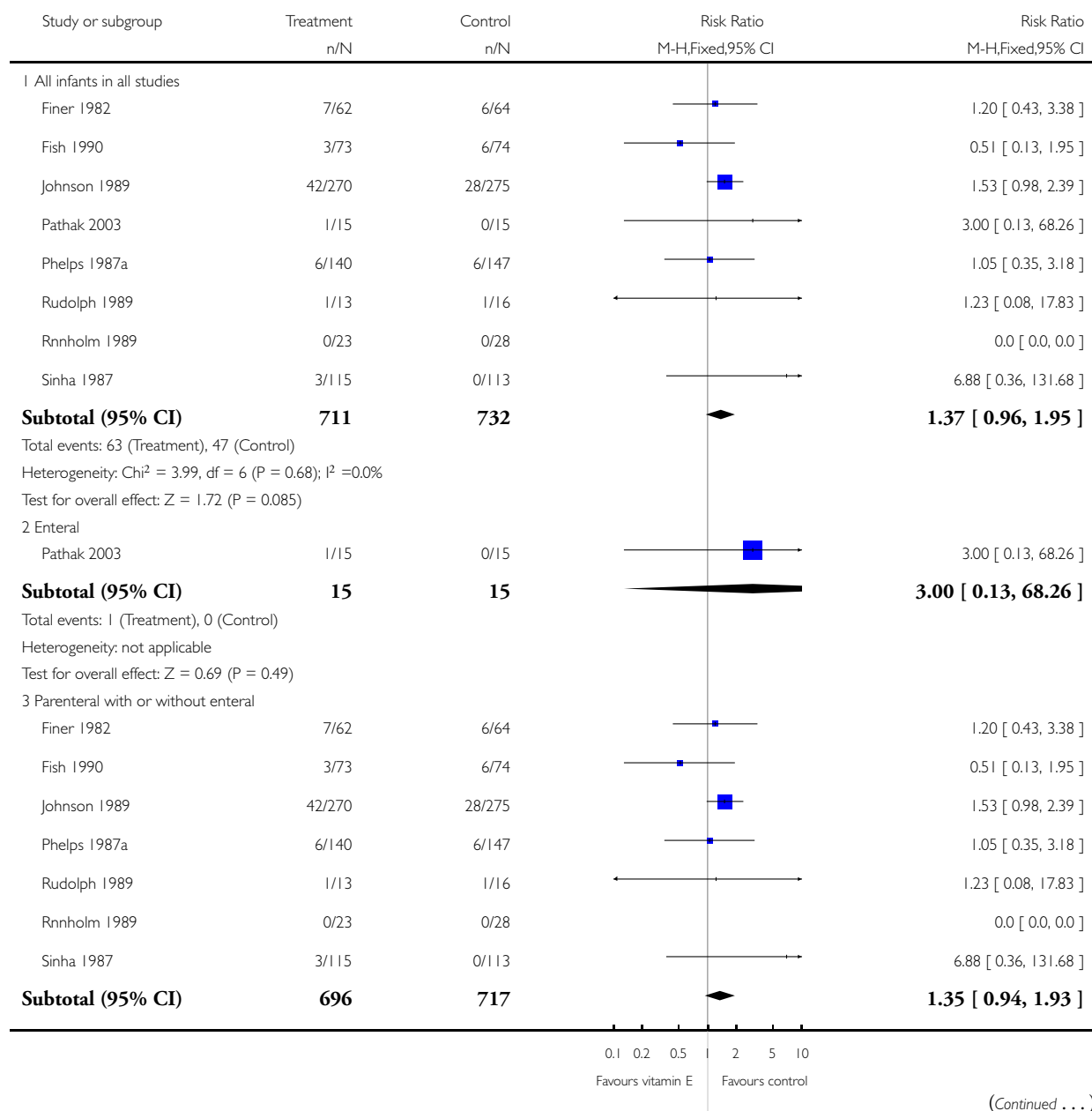


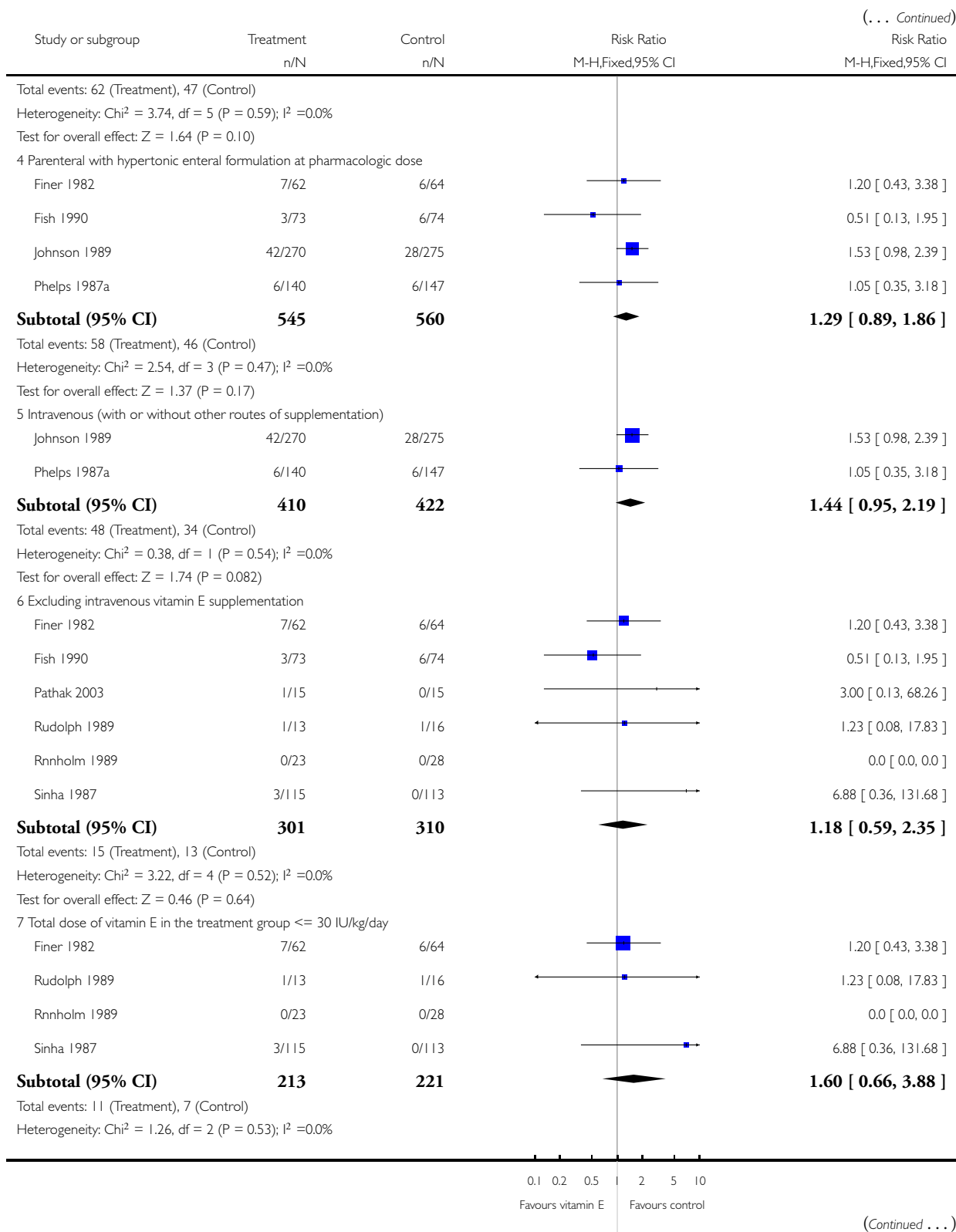
# **Analysis I.44. Comparison I Vitamin E versus placebo or no vitamin E, Outcome 44 Necrotizing enterocolitis.**

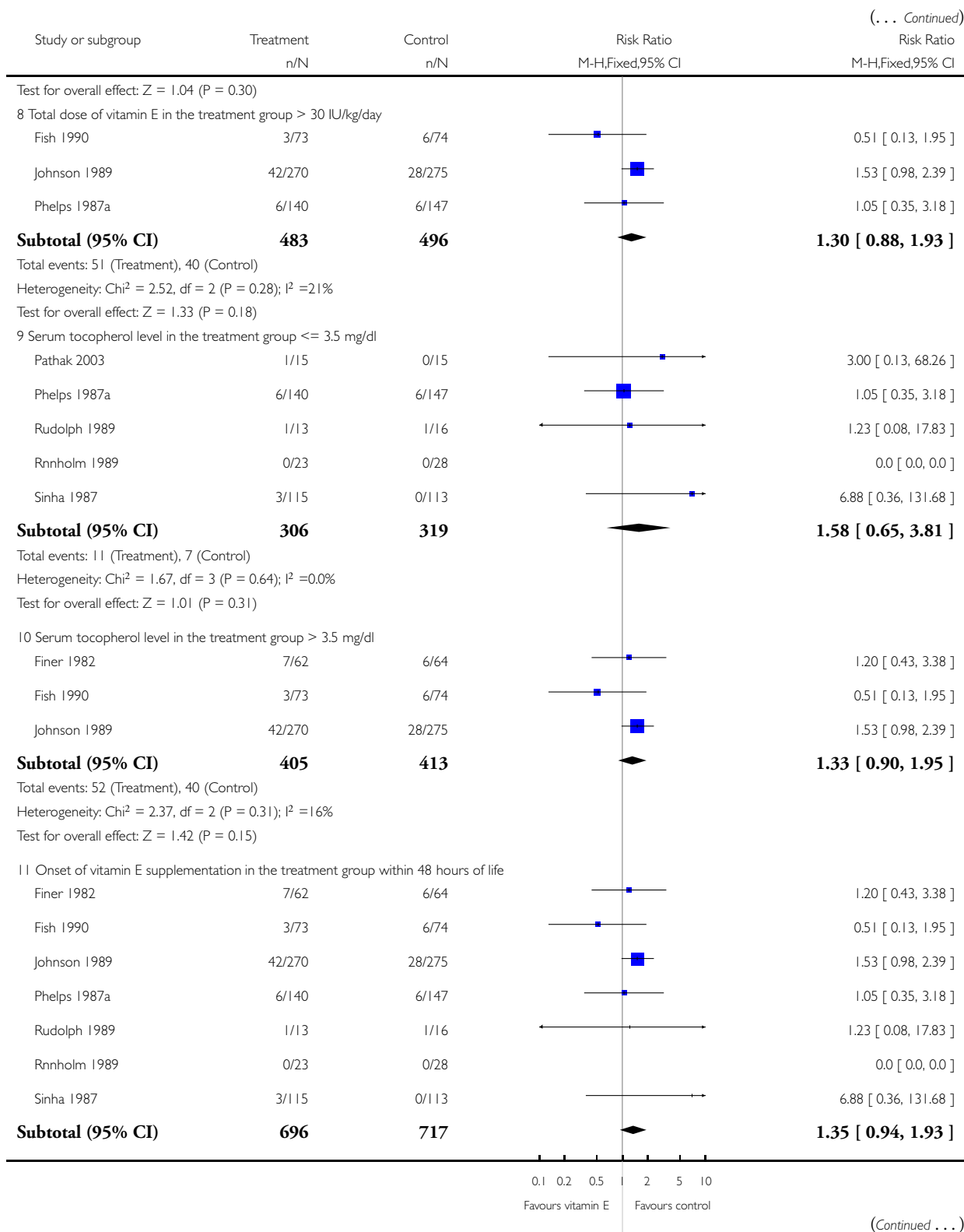
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

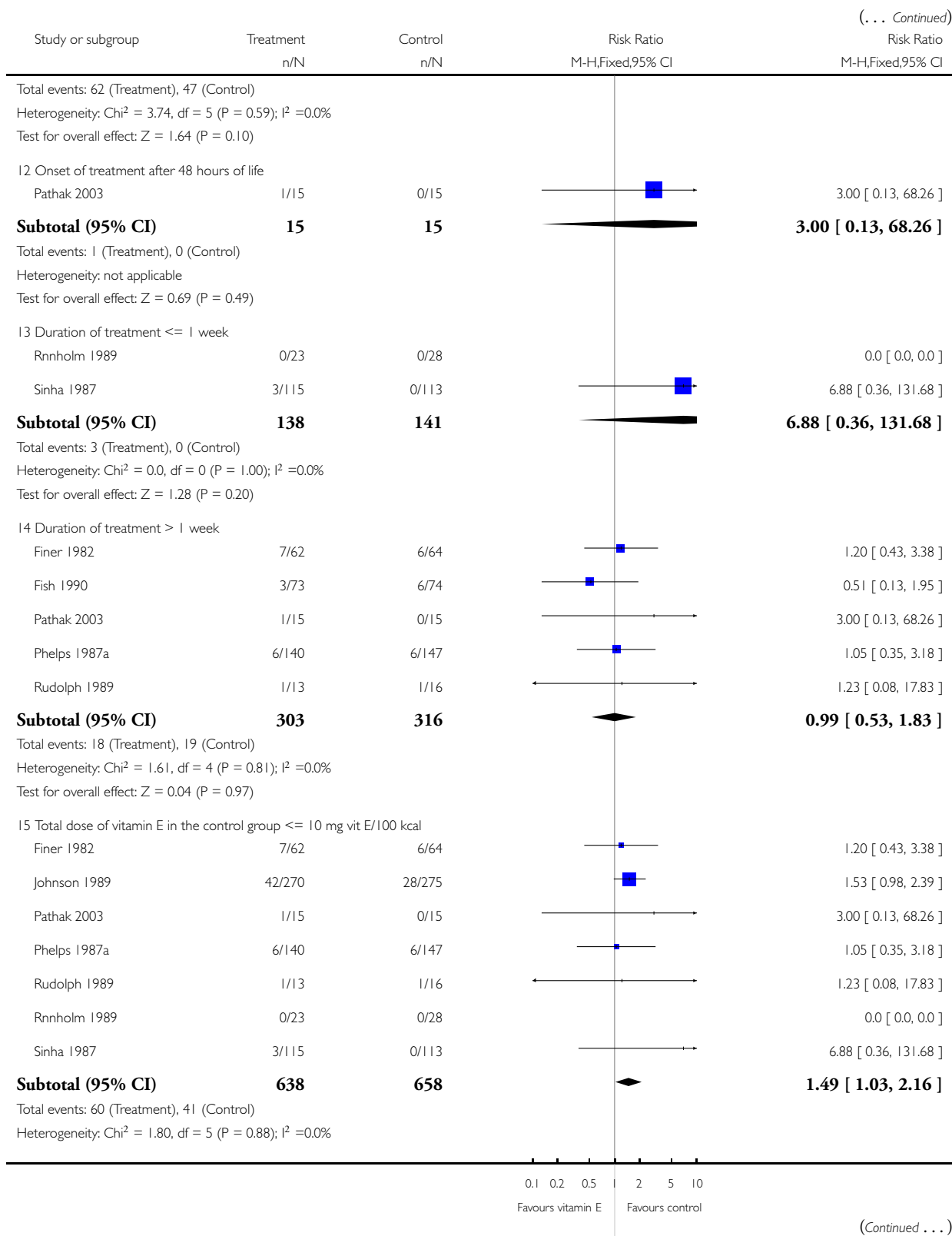
Comparison: I Vitamin E versus placebo or no vitamin E

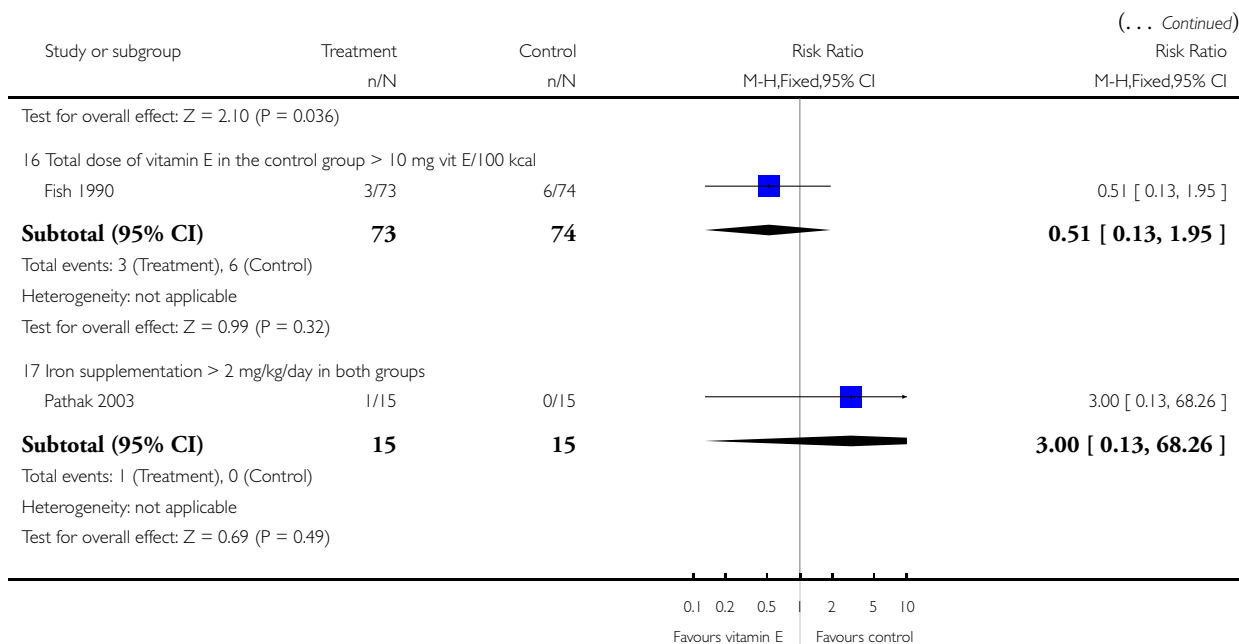
Outcome: 44 Necrotizing enterocolitis









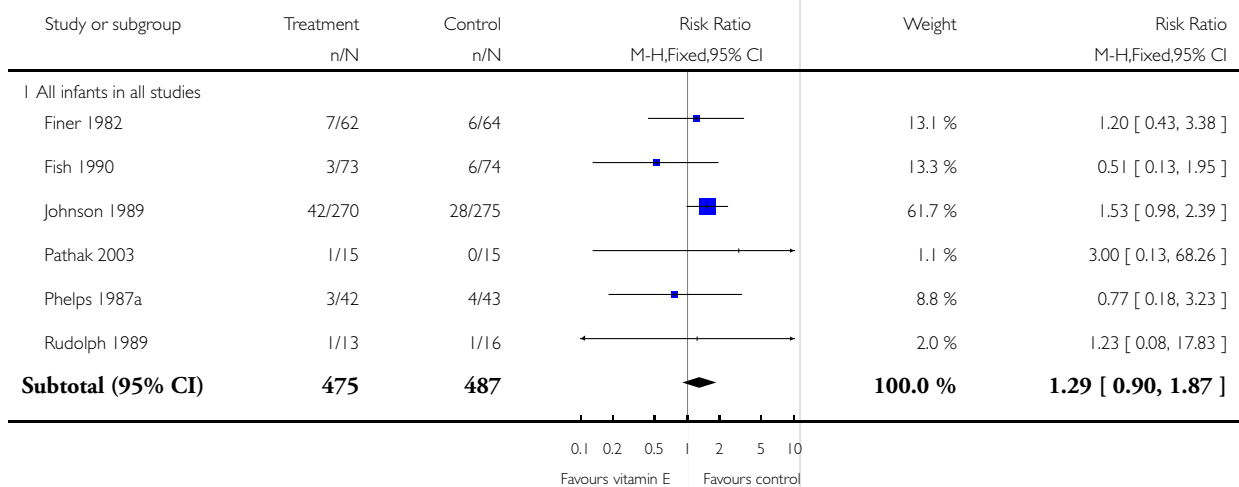


#### Analysis 1.45. Comparison I Vitamin E versus placebo or no vitamin E, Outcome 45 Necrotizing enterocolitis among very low birth weight infants.

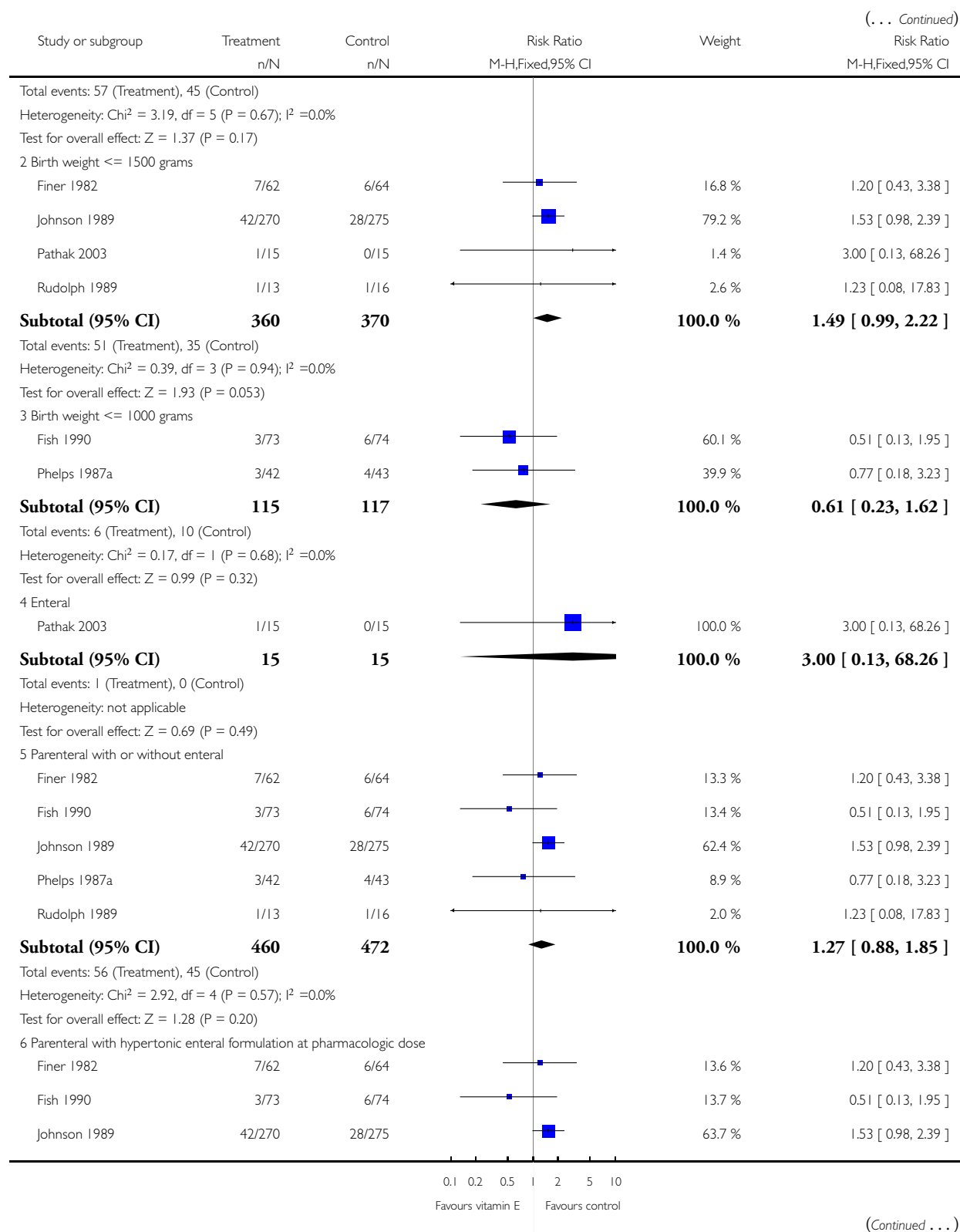
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: I Vitamin E versus placebo or no vitamin E

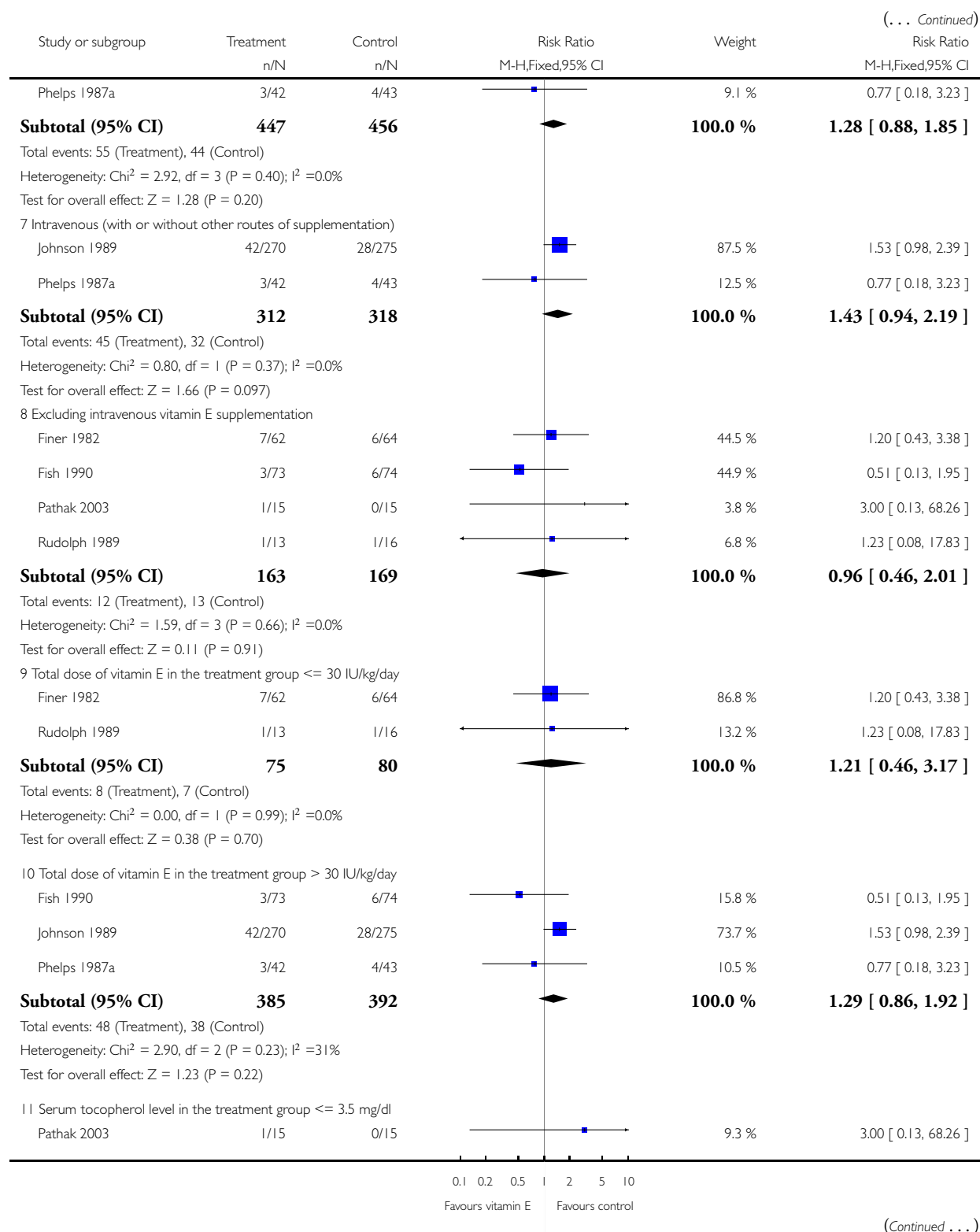
Outcome: 45 Necrotizing enterocolitis among very low birth weight infants

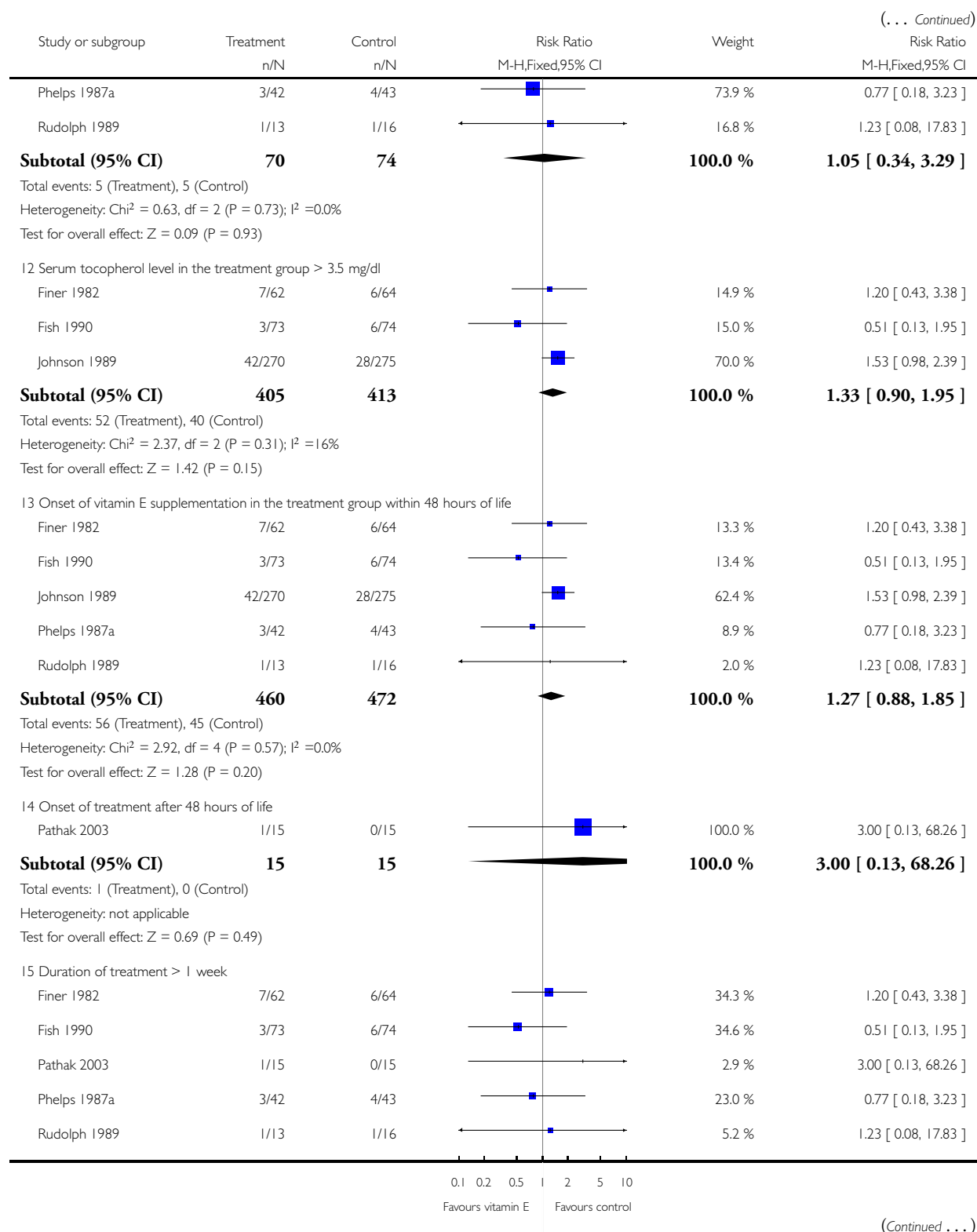


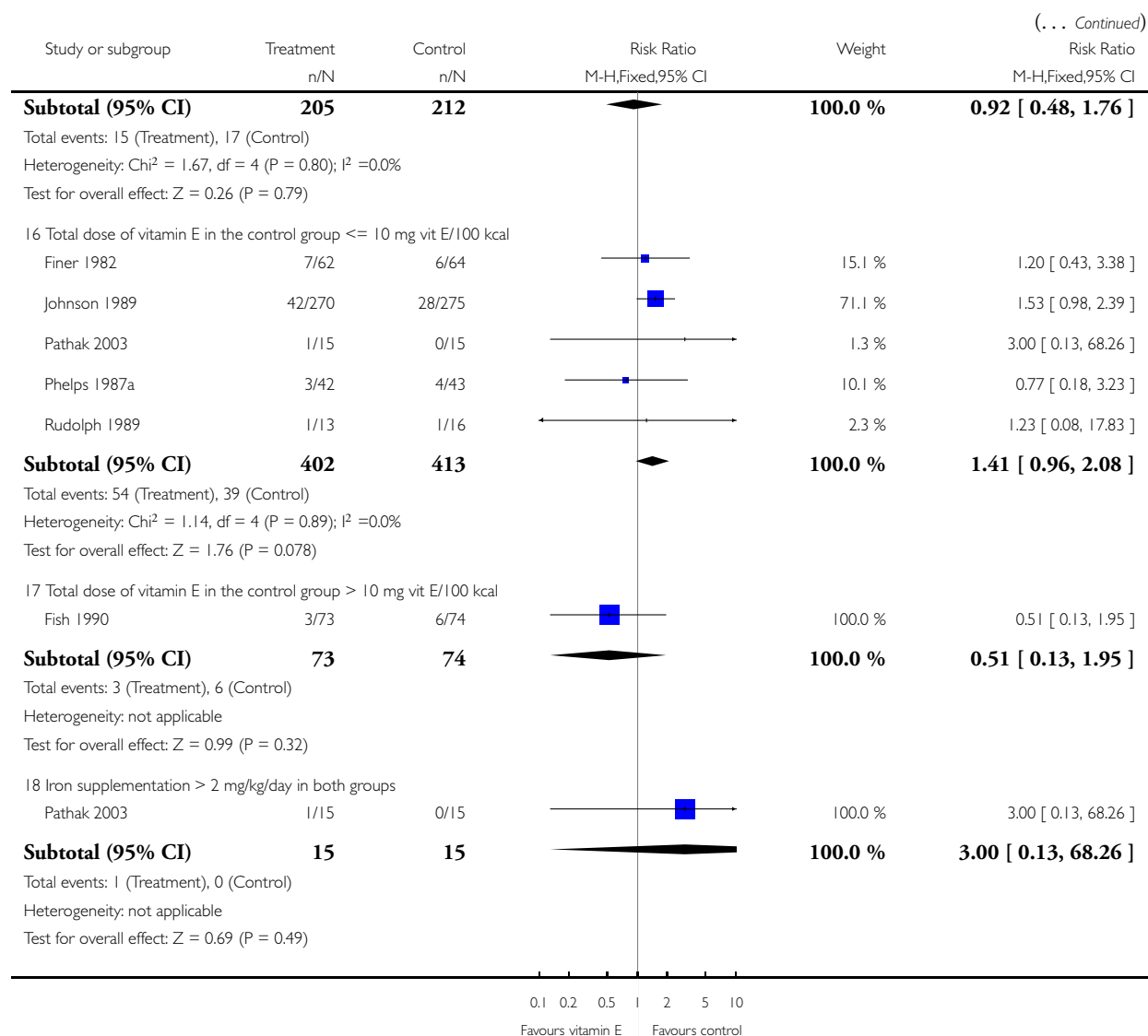
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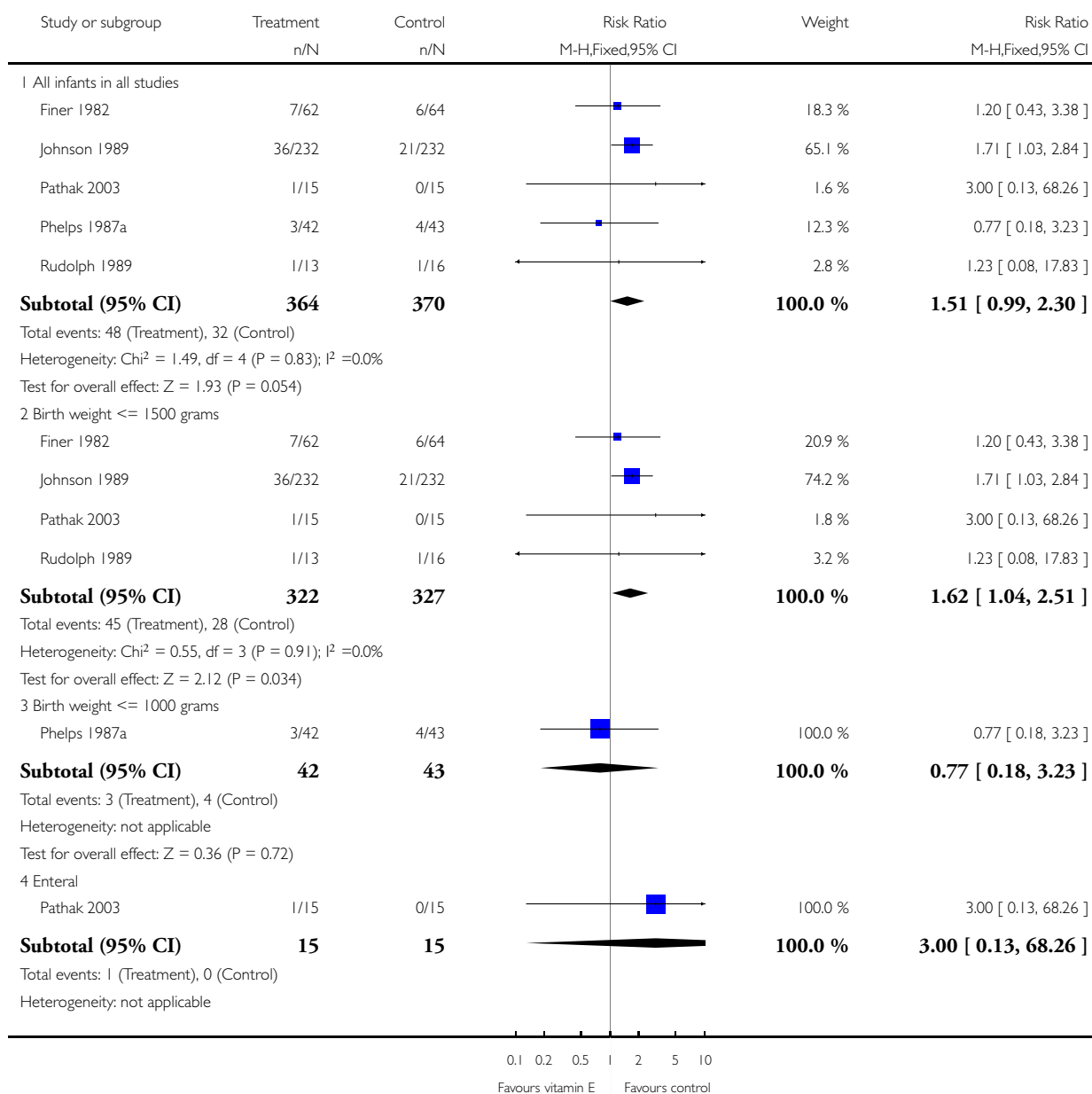


# **Analysis 1.46. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 46 Necrotizing enterocolitis among very low birth weight infants treated for > 1 week.**

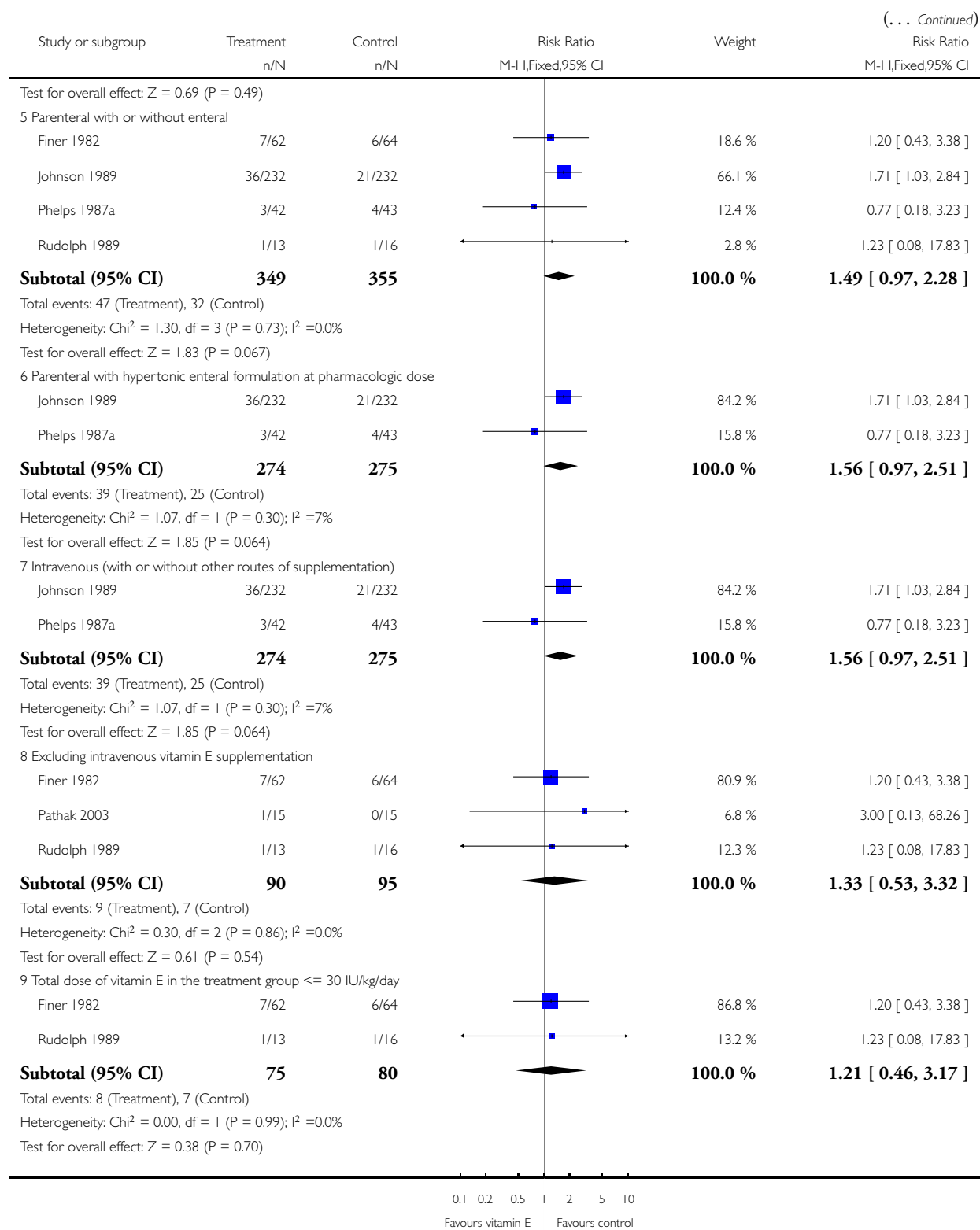
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

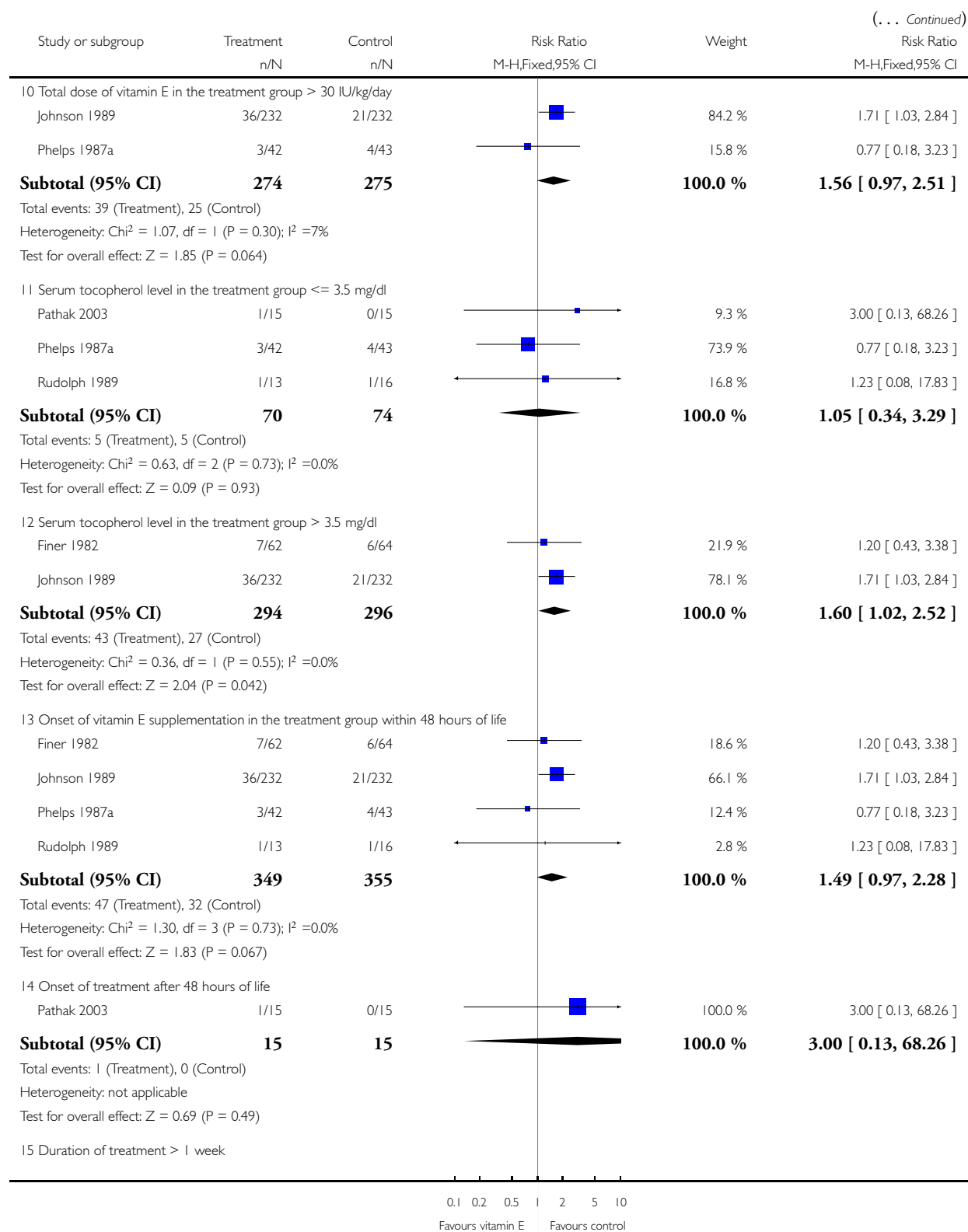
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 46 Necrotizing enterocolitis among very low birth weight infants treated for > 1 week

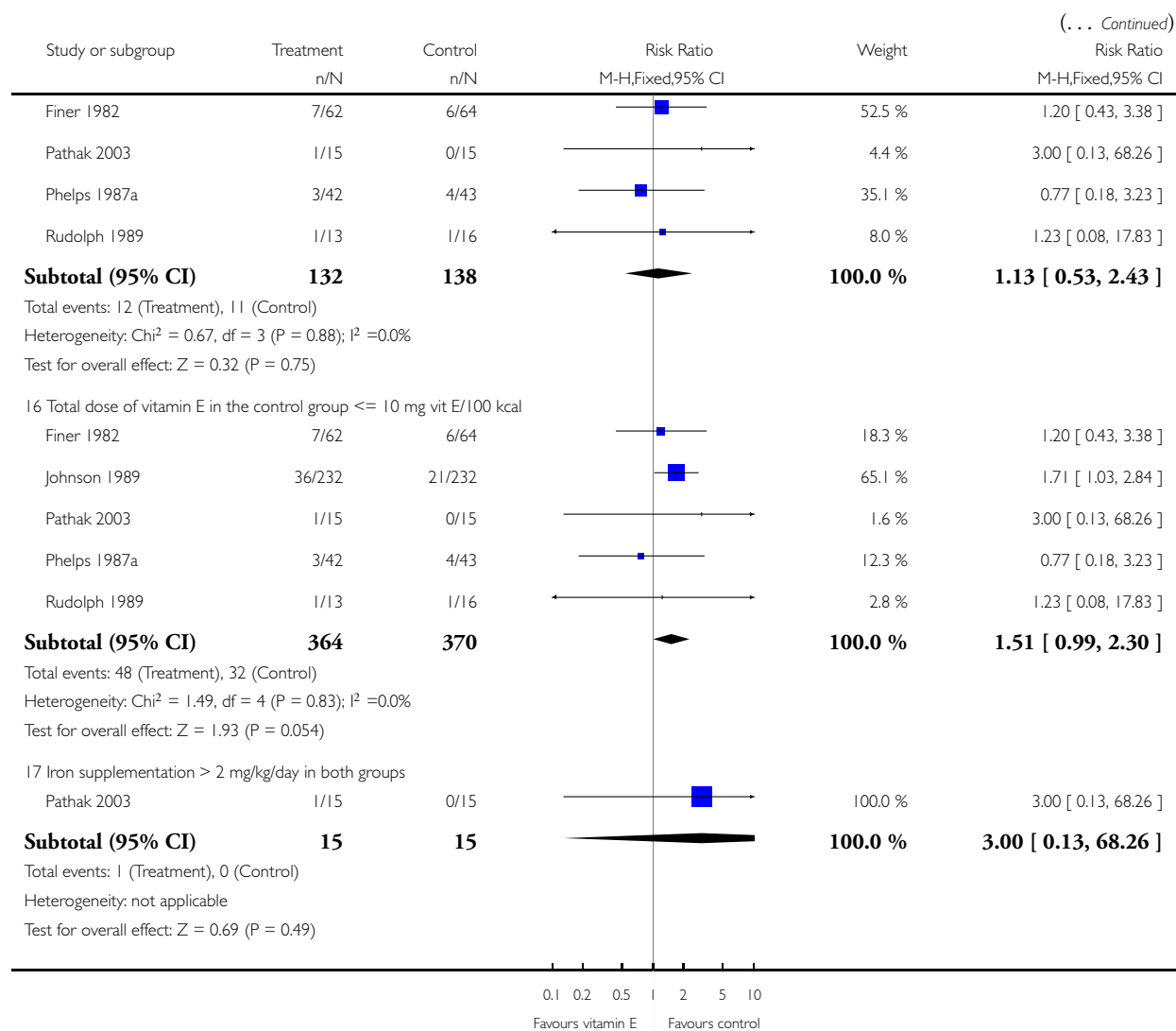


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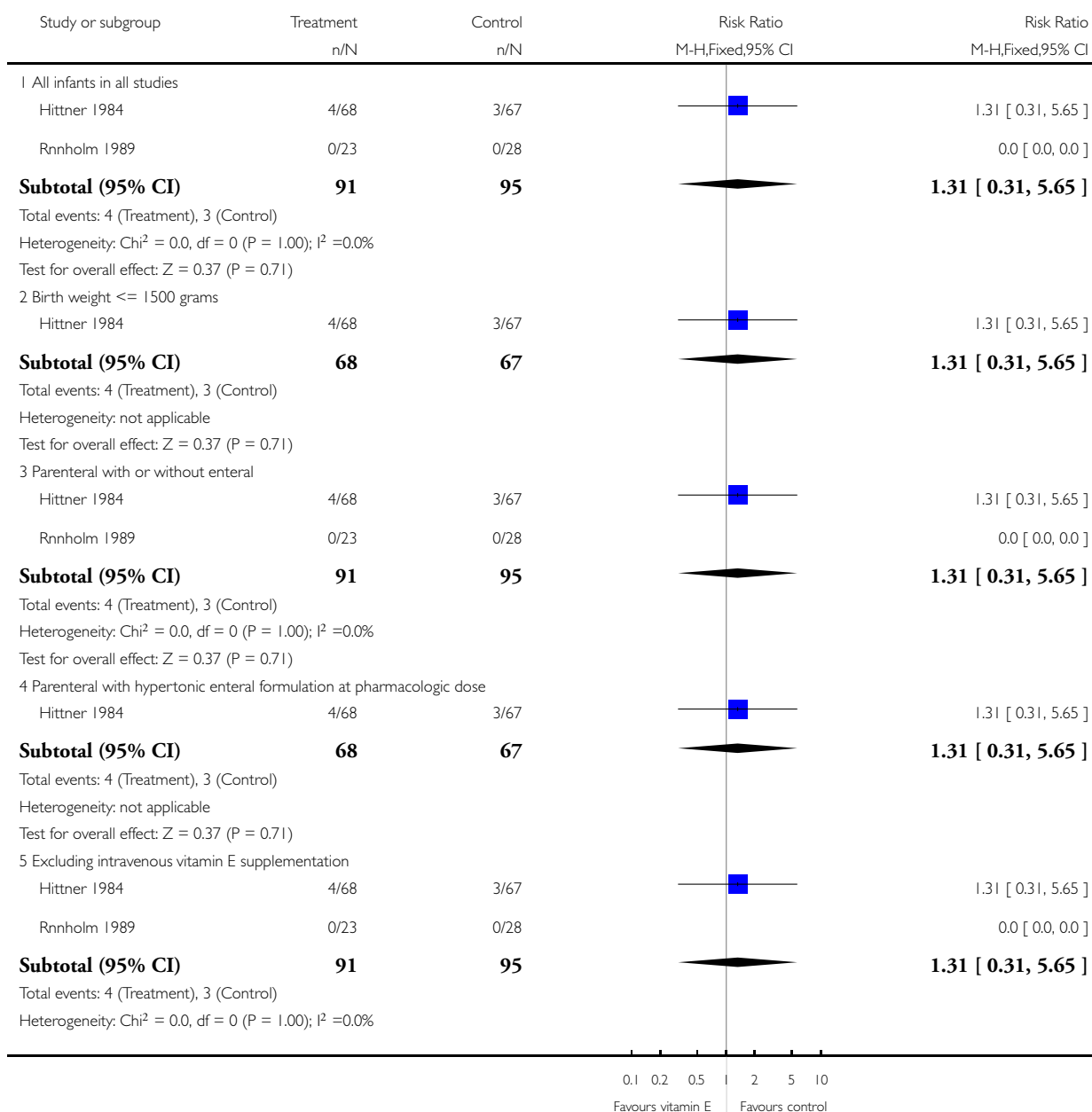


# **Analysis I.47. Comparison I Vitamin E versus placebo or no vitamin E, Outcome 47 Necrotizing enterocolitis among survivors.**

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

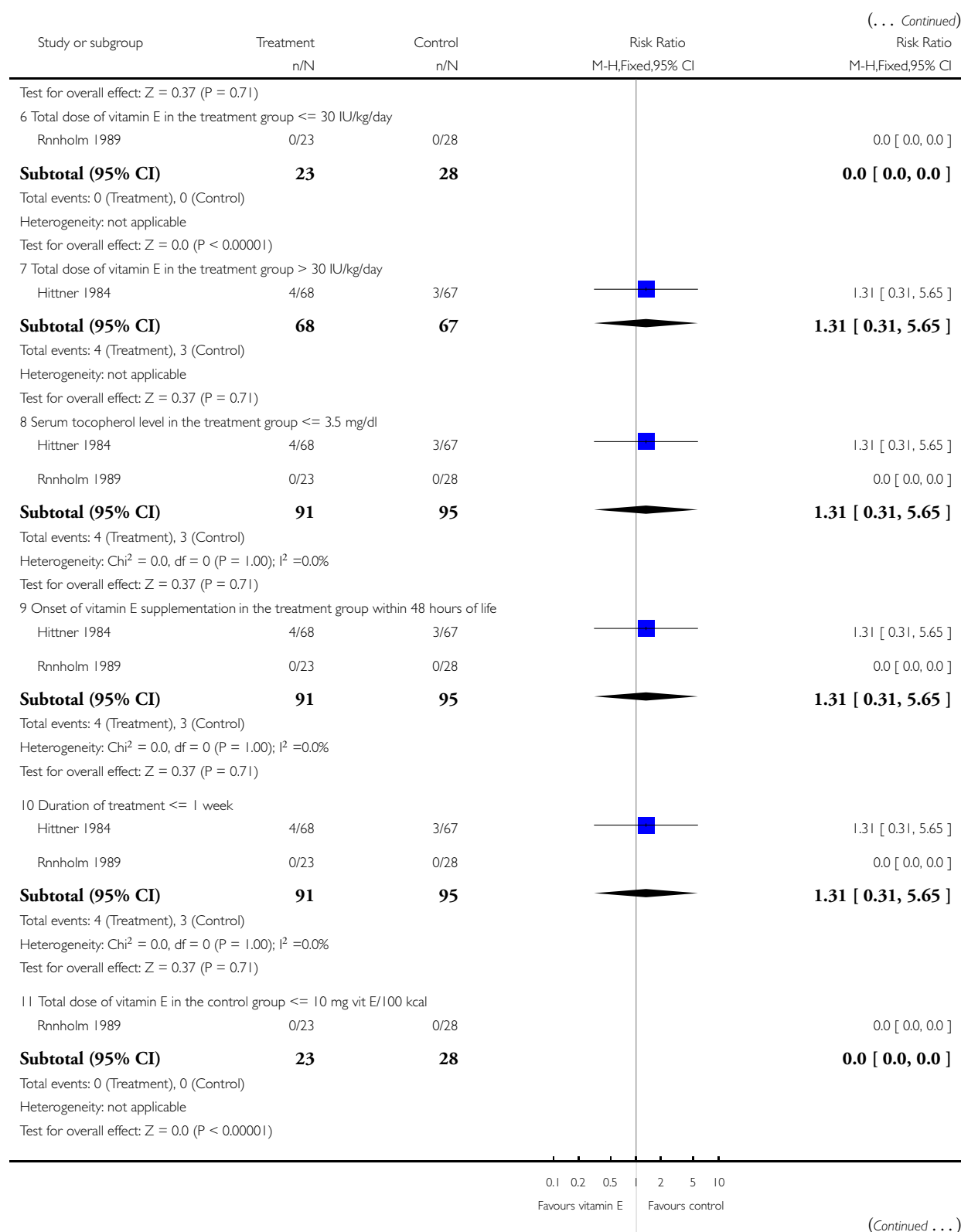
Comparison: I Vitamin E versus placebo or no vitamin E

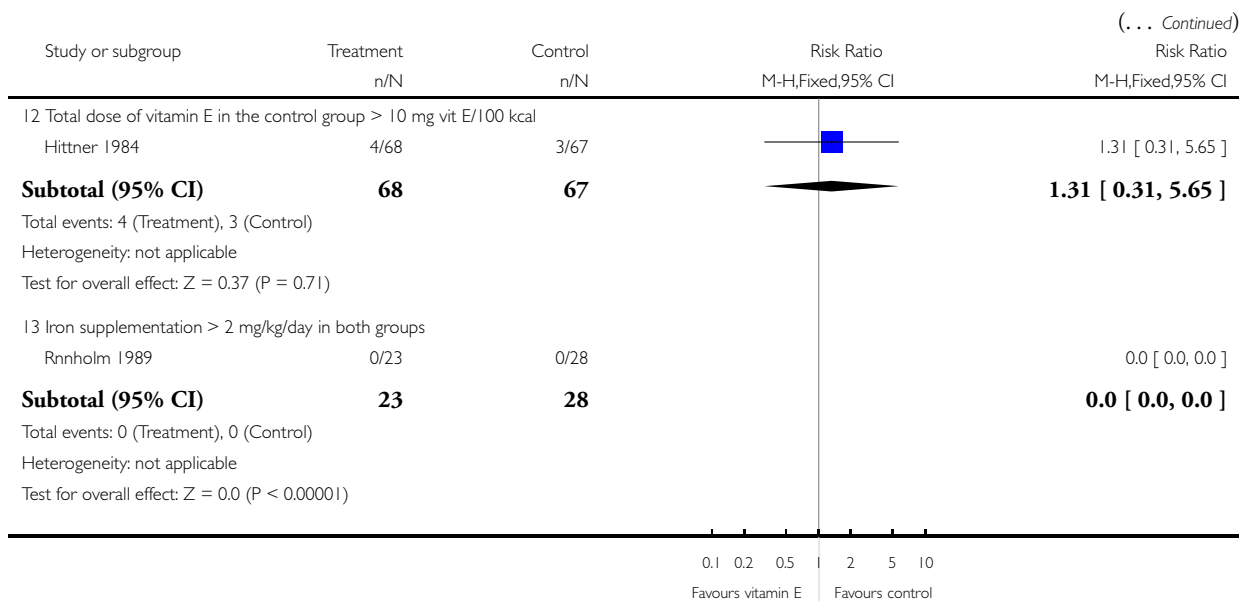
Outcome: 47 Necrotizing enterocolitis among survivors



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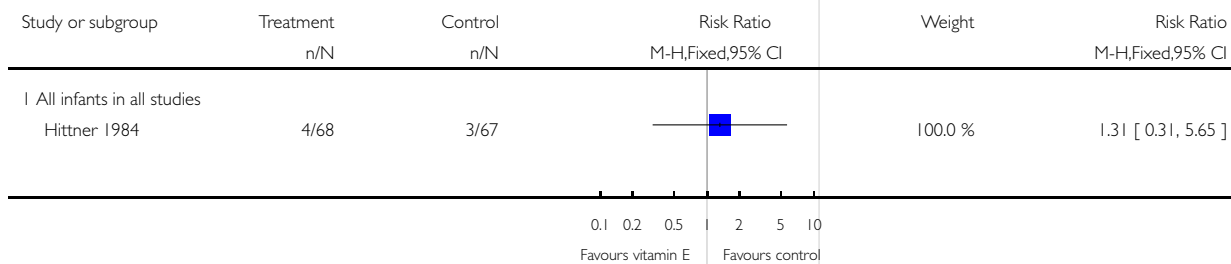


#### Analysis I.48. Comparison I Vitamin E versus placebo or no vitamin E, Outcome 48 Necrotizing enterocolitis among surviving very low birth weight infants.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: I Vitamin E versus placebo or no vitamin E

Outcome: 48 Necrotizing enterocolitis among surviving very low birth weight infants

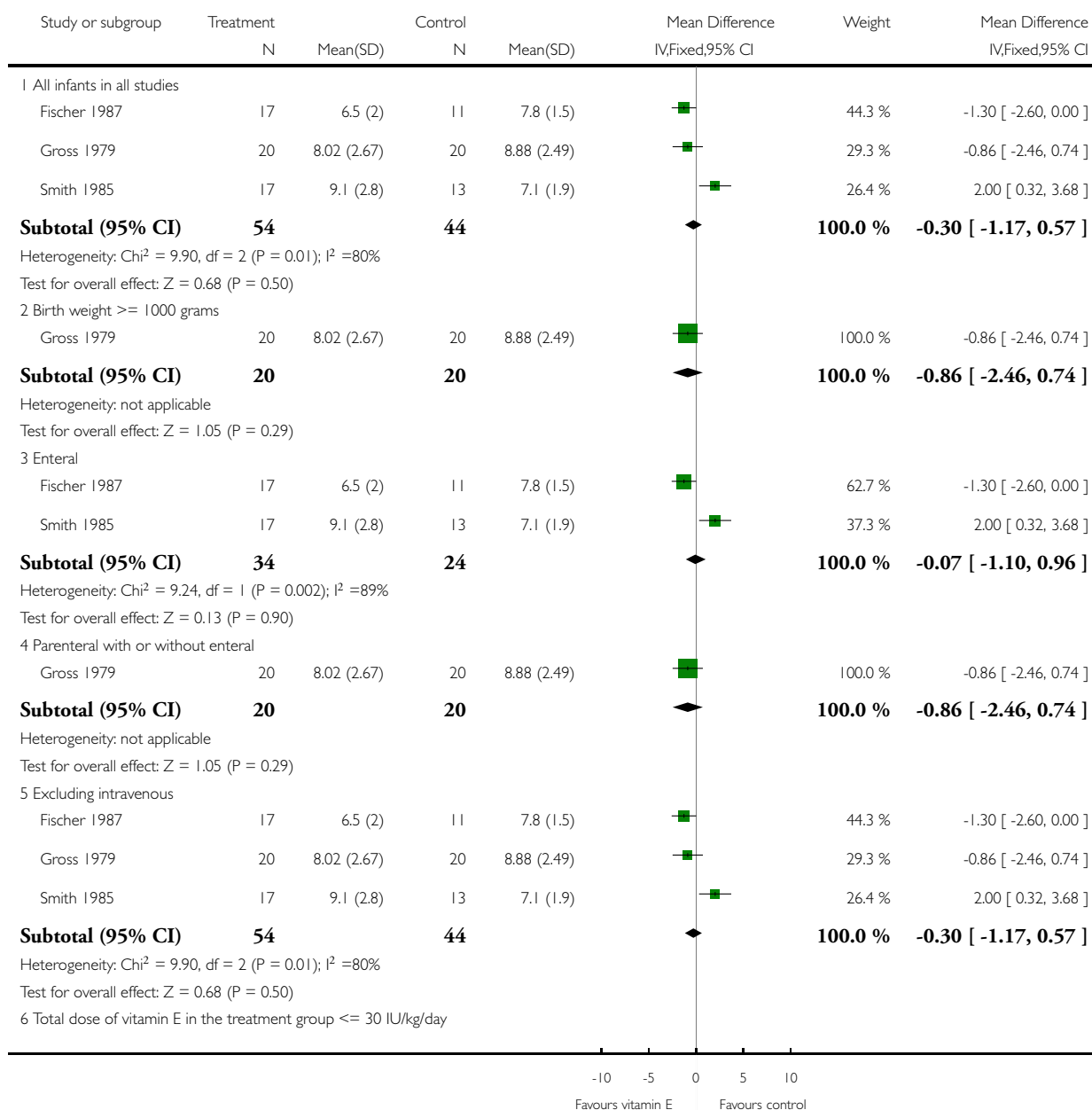


### Analysis 1.49. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 49 Serum bilirubin concentration (mg/100 ml) on day 3-5.

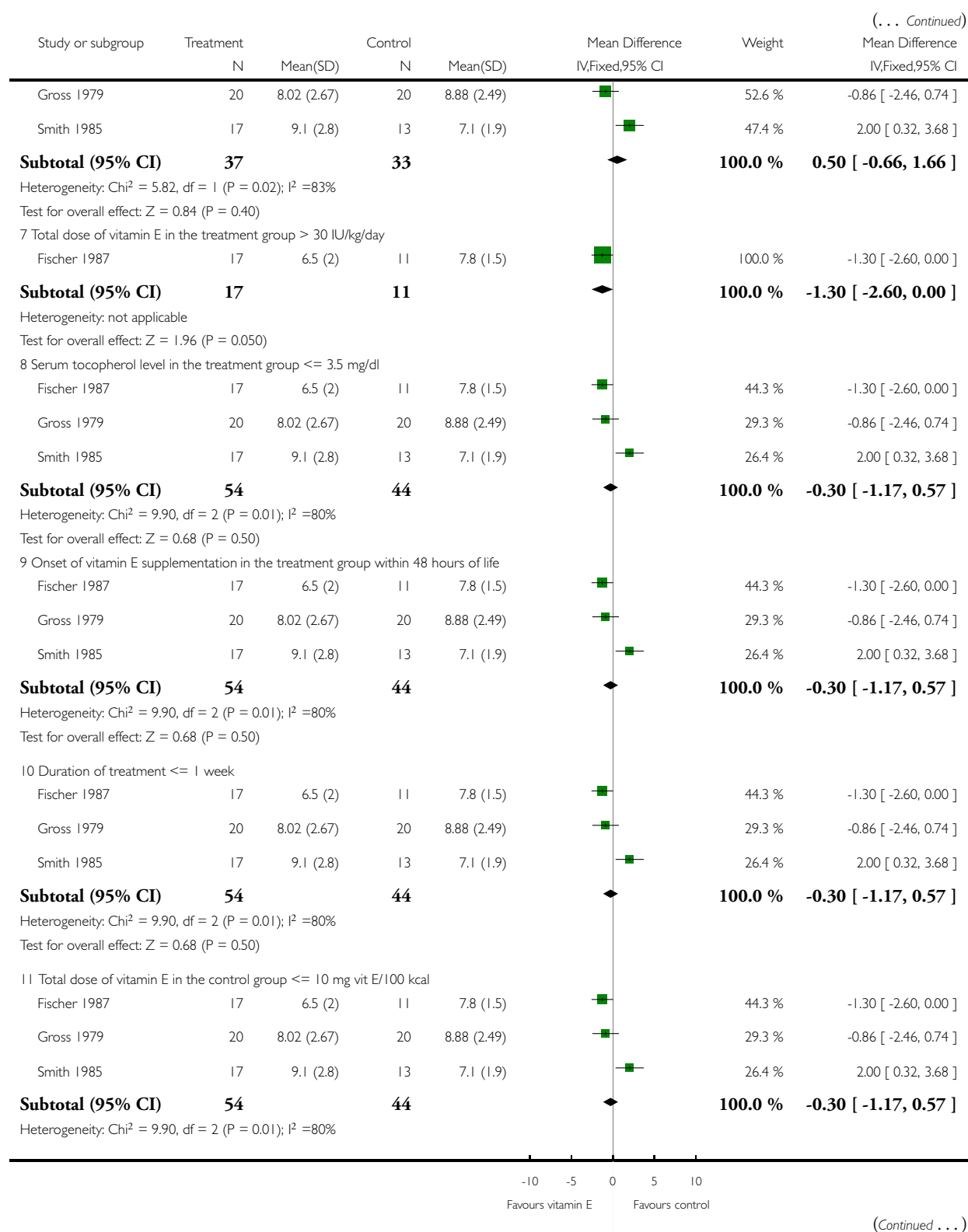
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

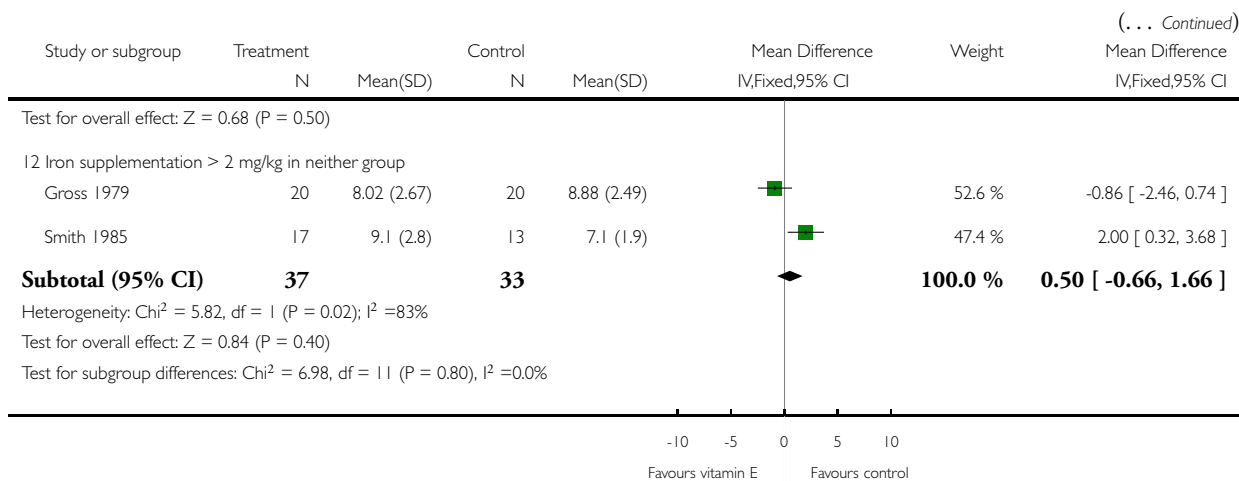
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 49 Serum bilirubin concentration (mg/100 ml) on day 3-5



(Continued ...)



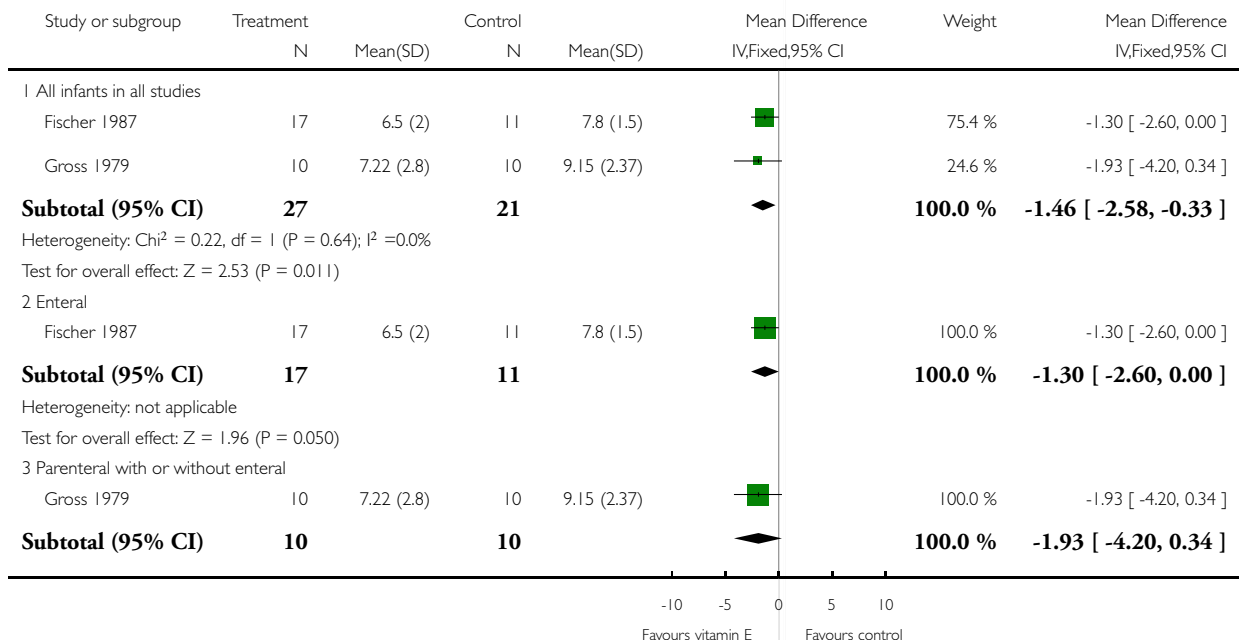


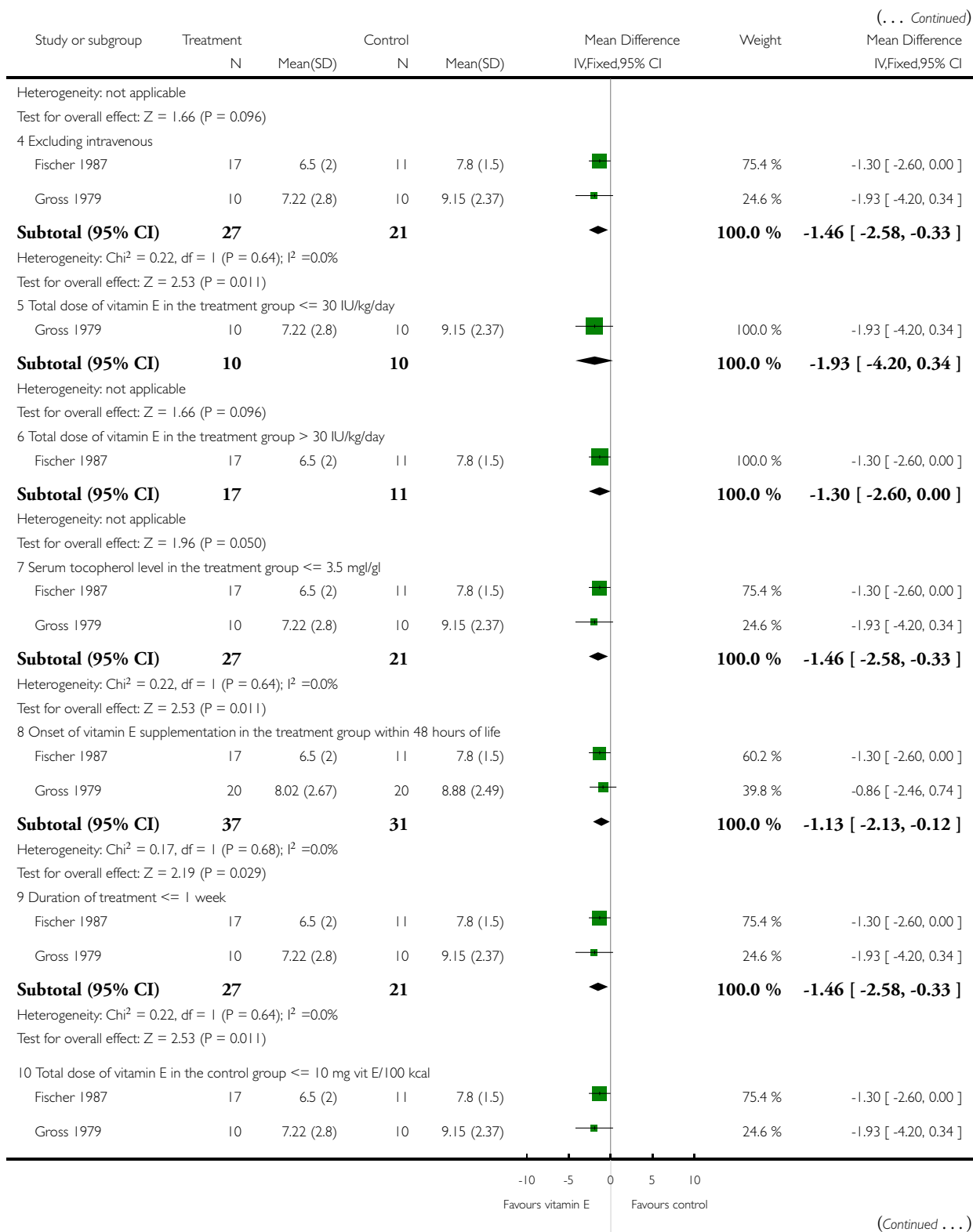
### Analysis 1.50. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 50 Serum bilirubin concentration in very low birth weight infants.

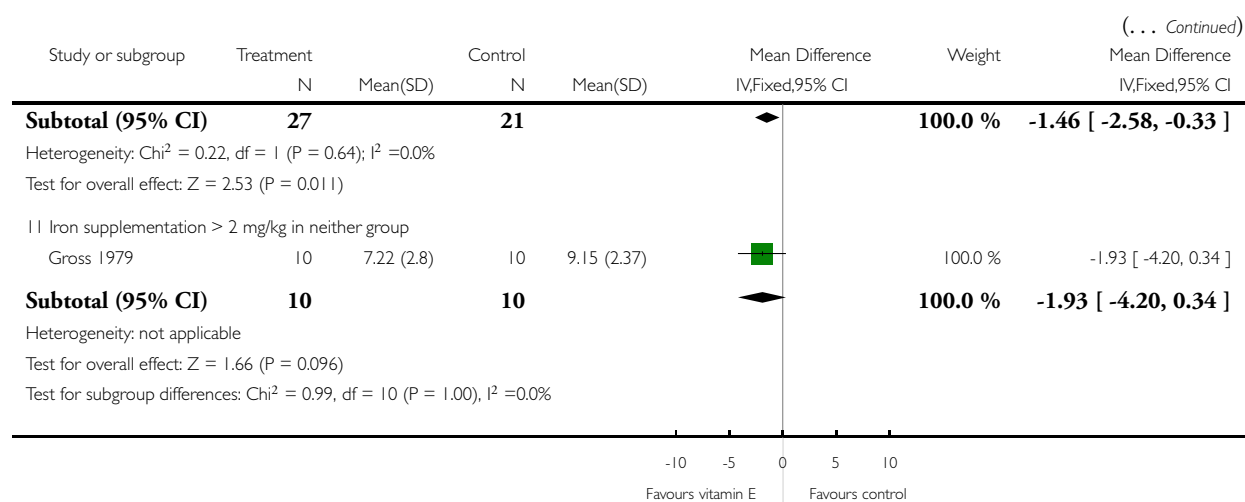
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 50 Serum bilirubin concentration in very low birth weight infants





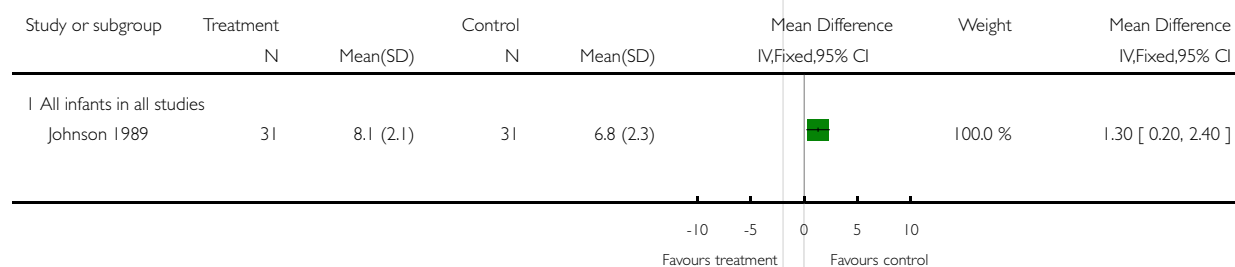


**Analysis 1.51. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 51 Serum bilirubin concentration on day 3-5 in a specific group (no hemolysis, polycythemia, prior transfus.**

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 51 Serum bilirubin concentration on day 3-5 in a specific group (no hemolysis, polycythemia, prior transfus

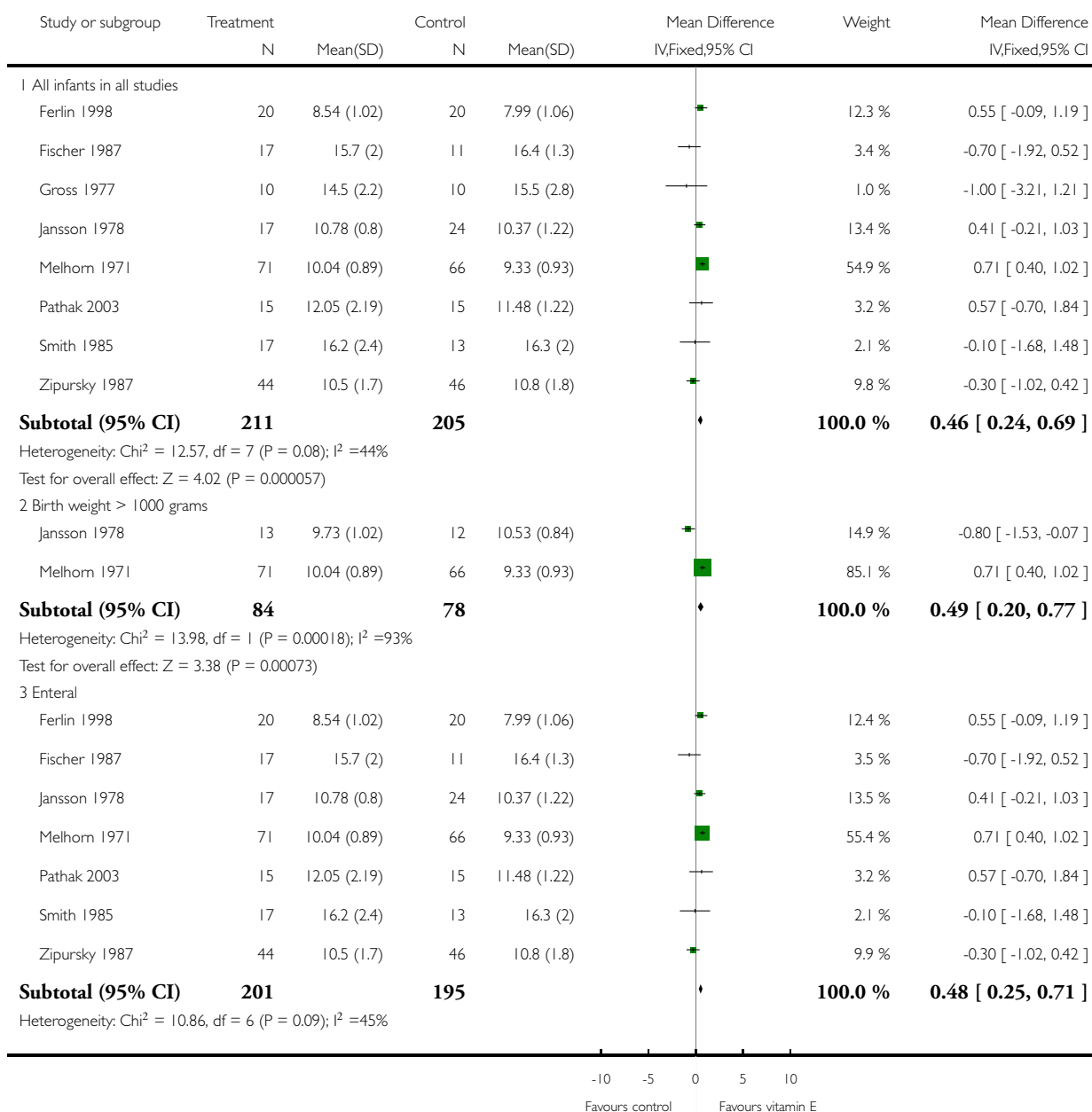


## Analysis 1.52. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 52 Hemoglobin concentration (g/100 ml).

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

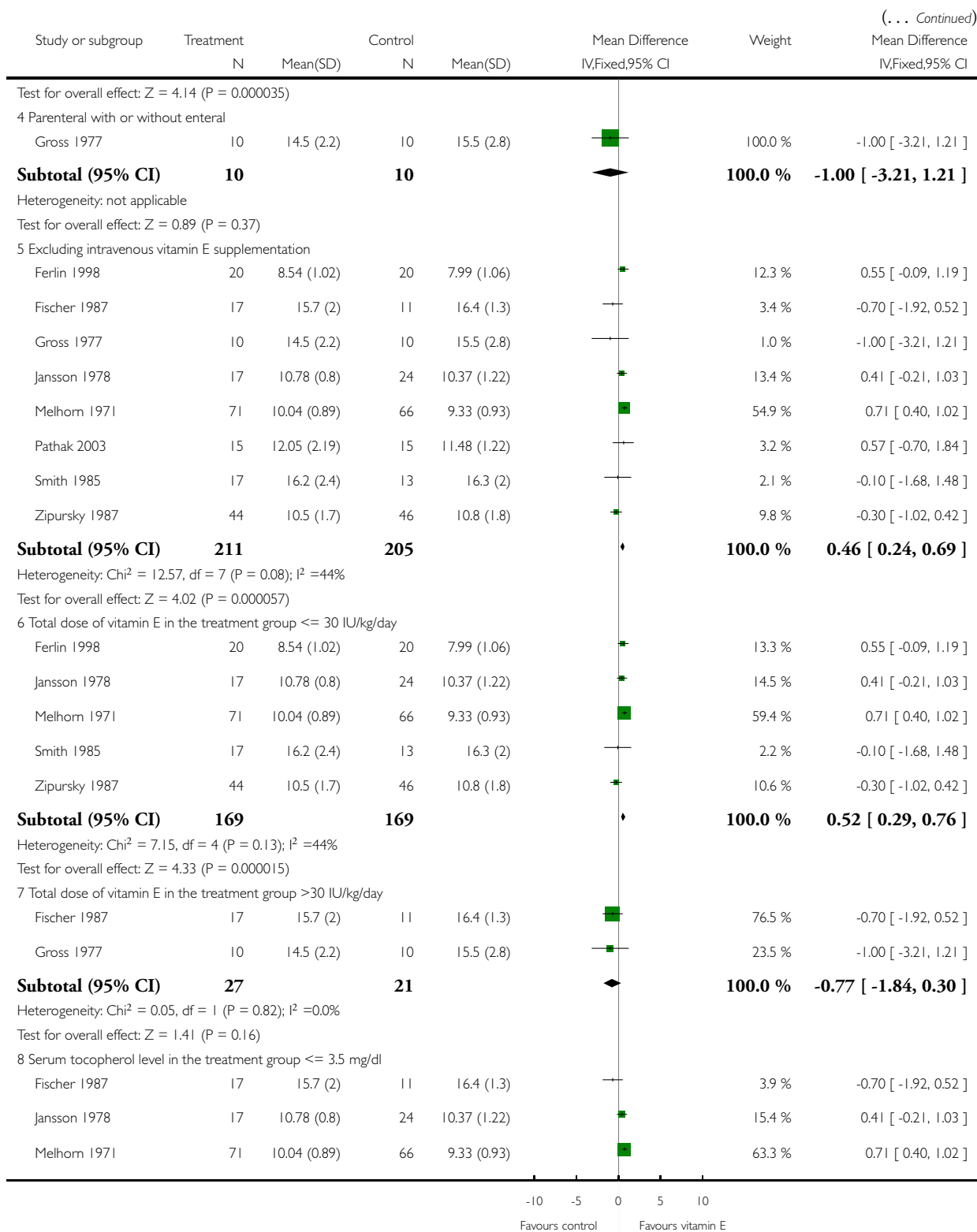
Comparison: 1 Vitamin E versus placebo or no vitamin E

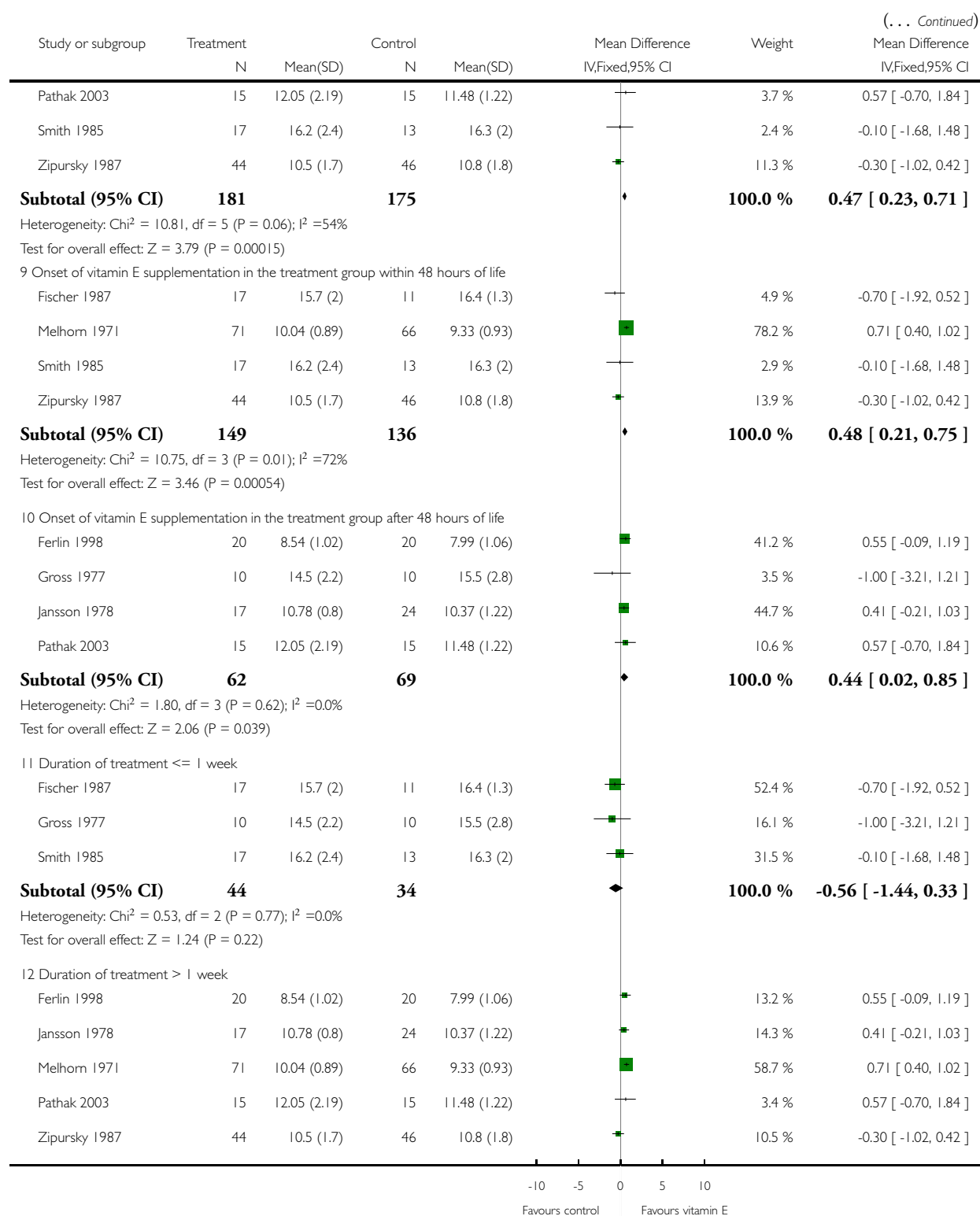
Outcome: 52 Hemoglobin concentration (g/100 ml)



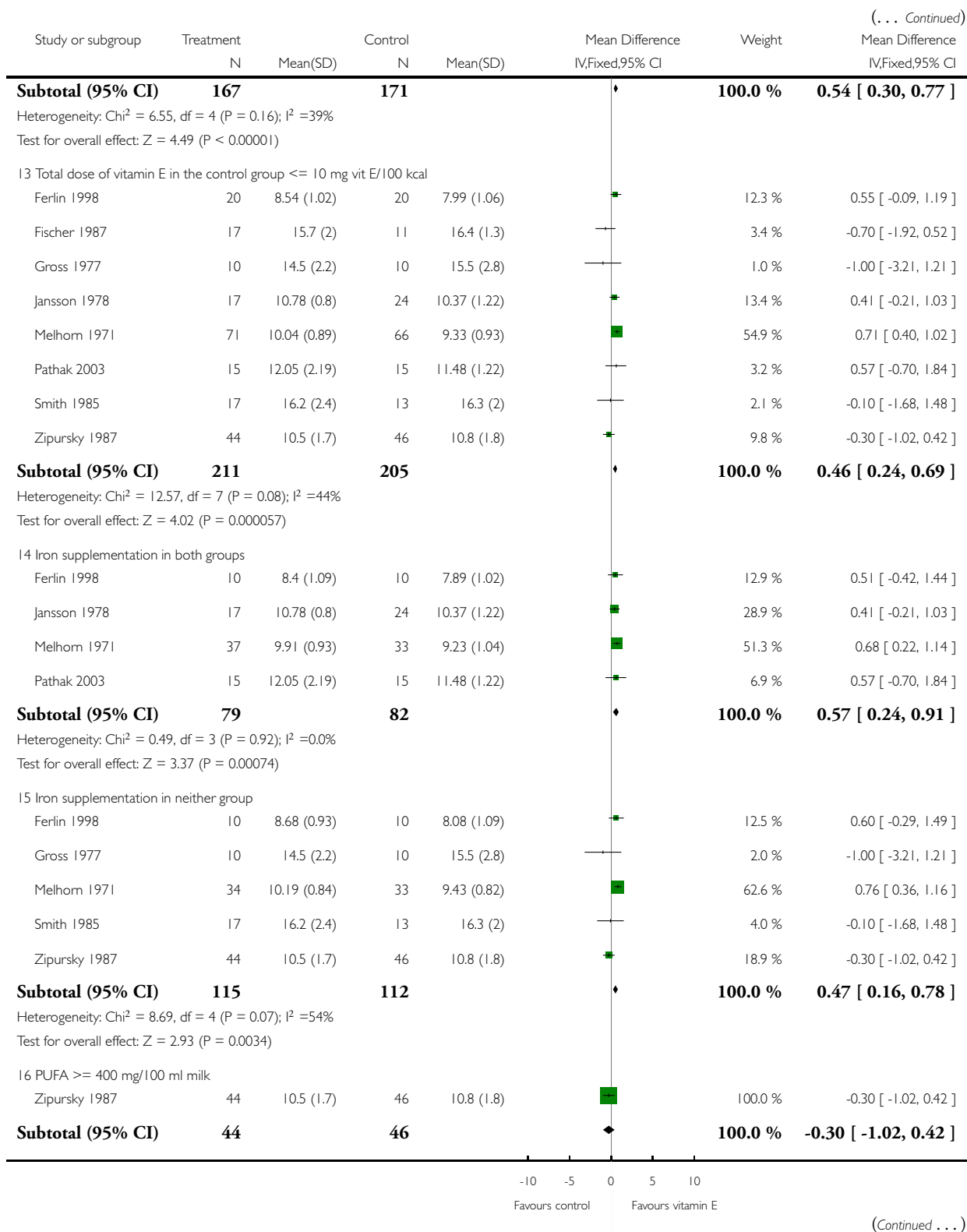
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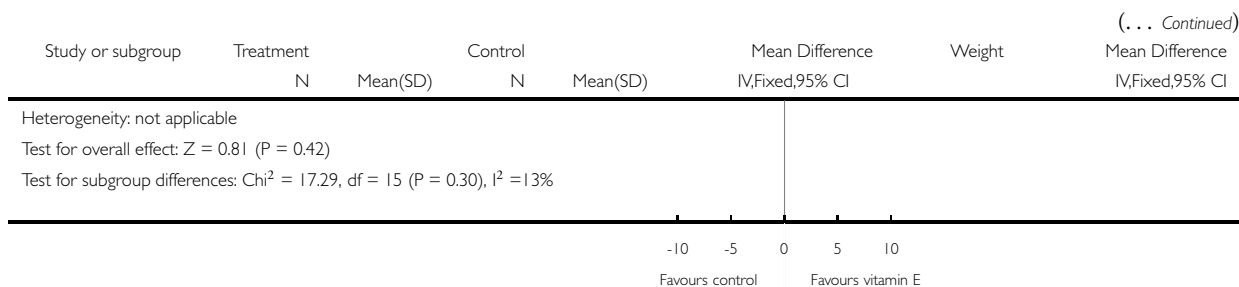






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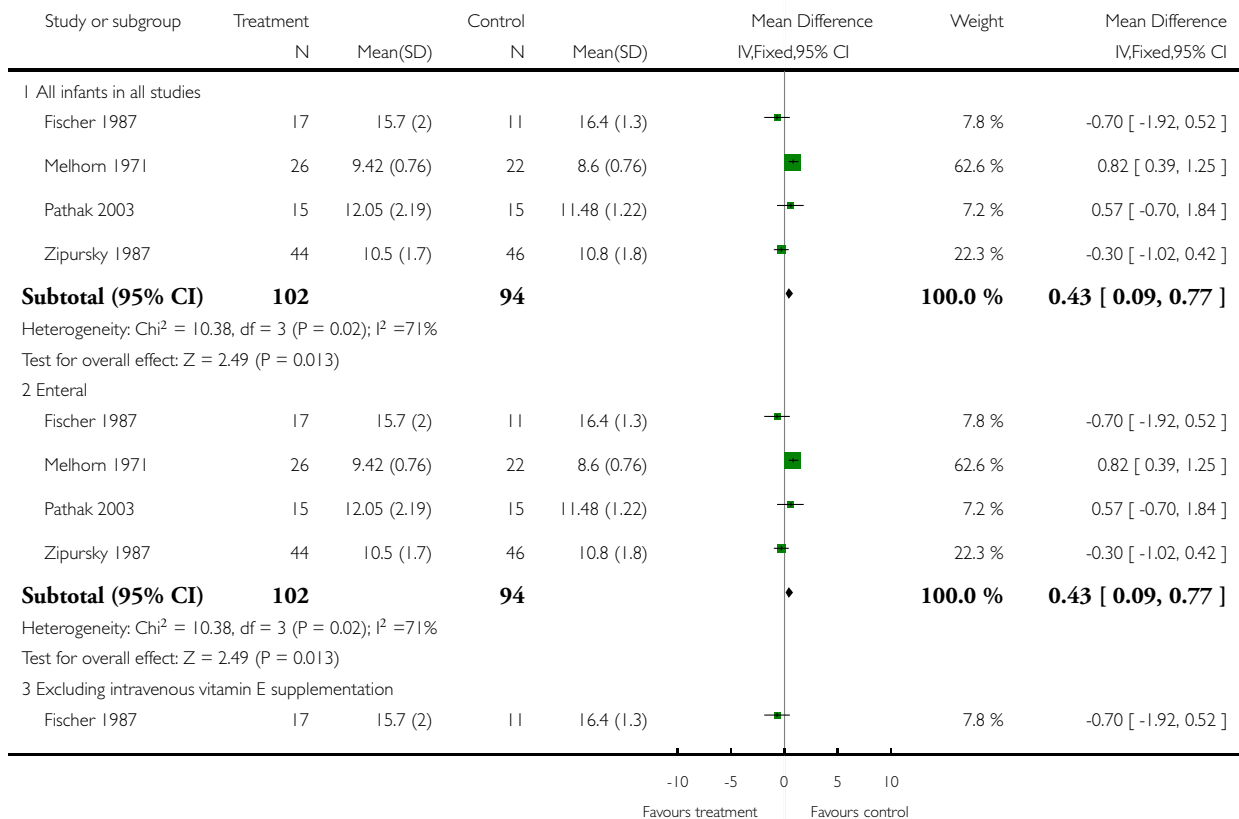


**Analysis 1.53. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 53 Hemoglobin concentration in very low birth weight infants.**

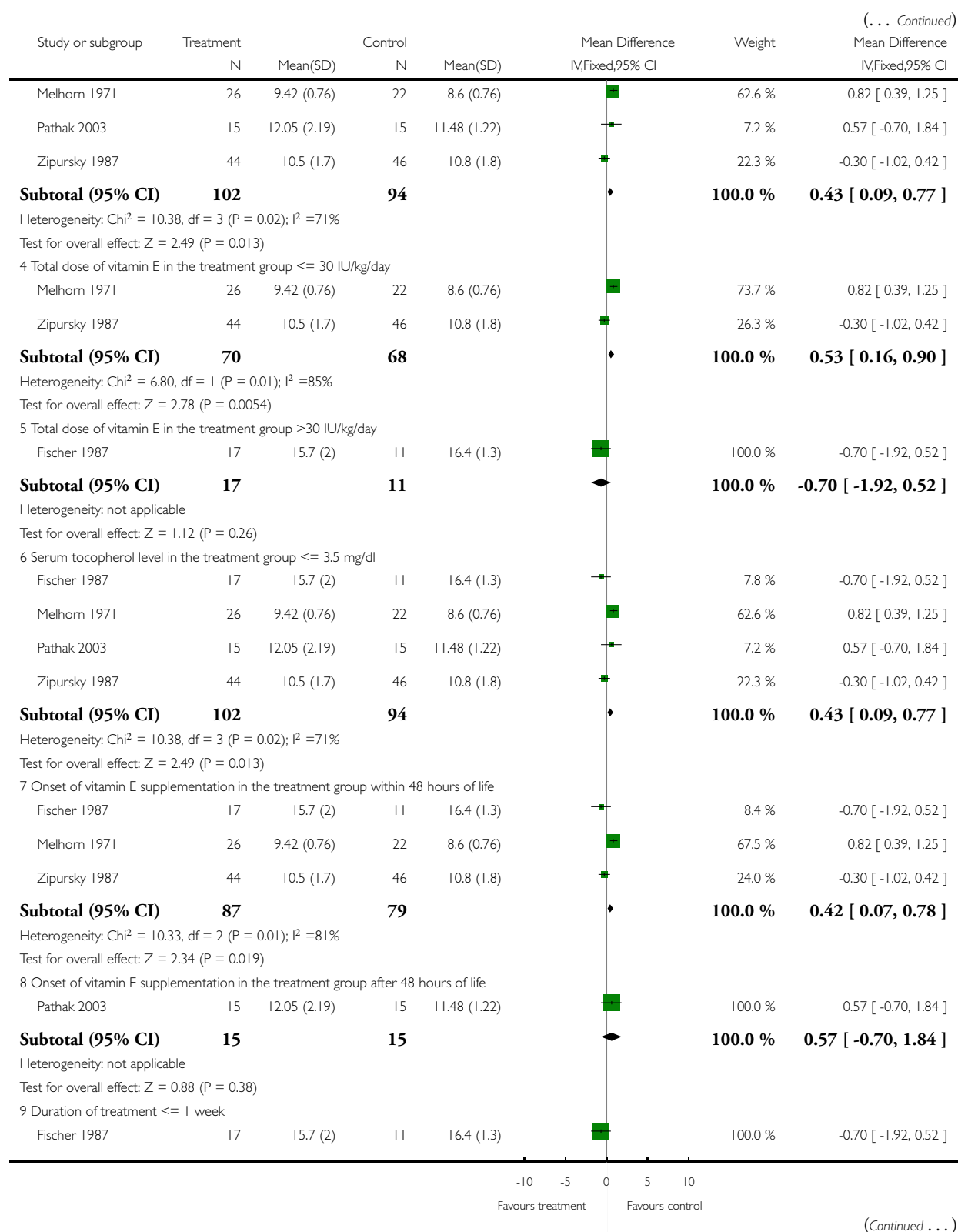
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

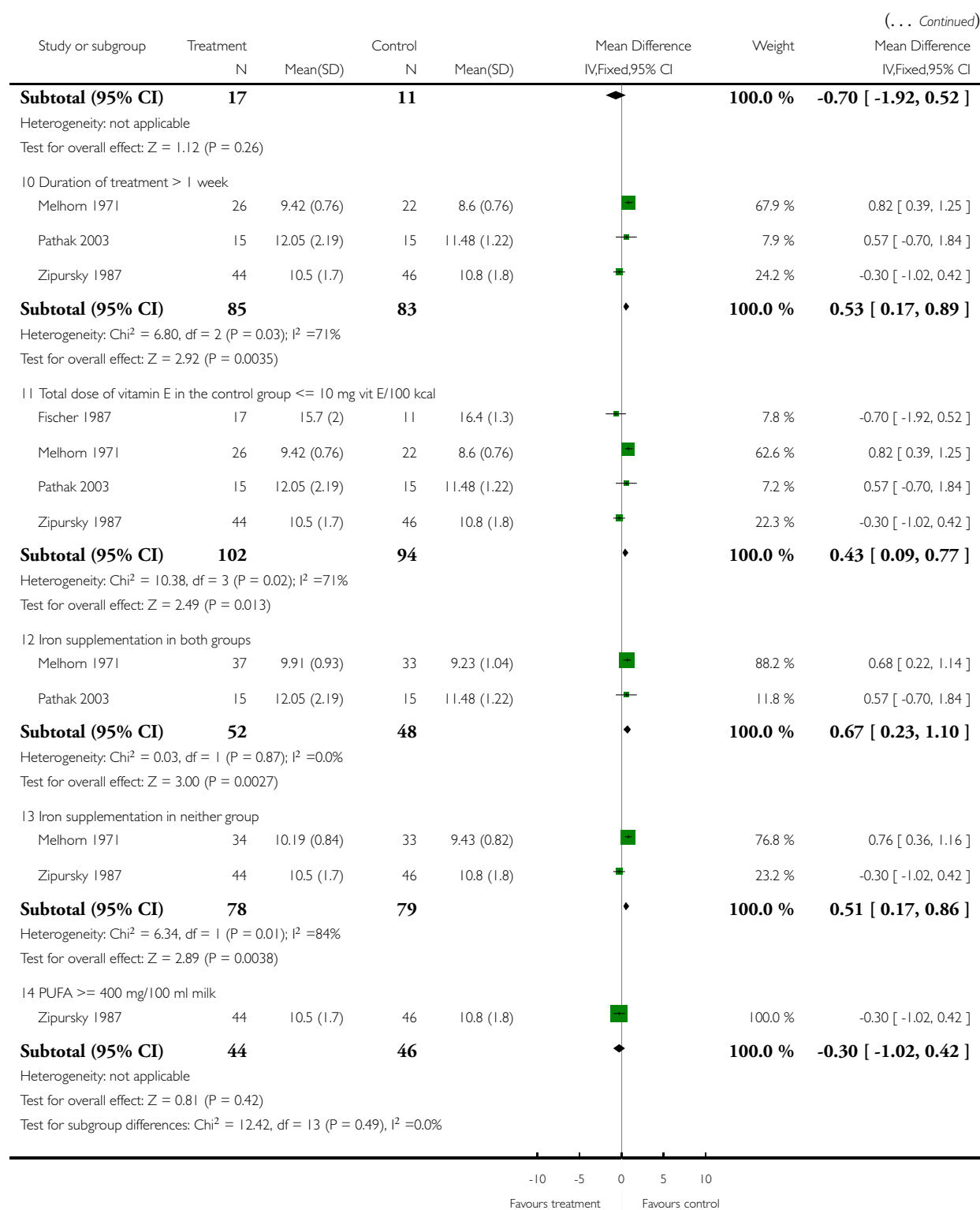
Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 53 Hemoglobin concentration in very low birth weight infants



(Continued . . .)



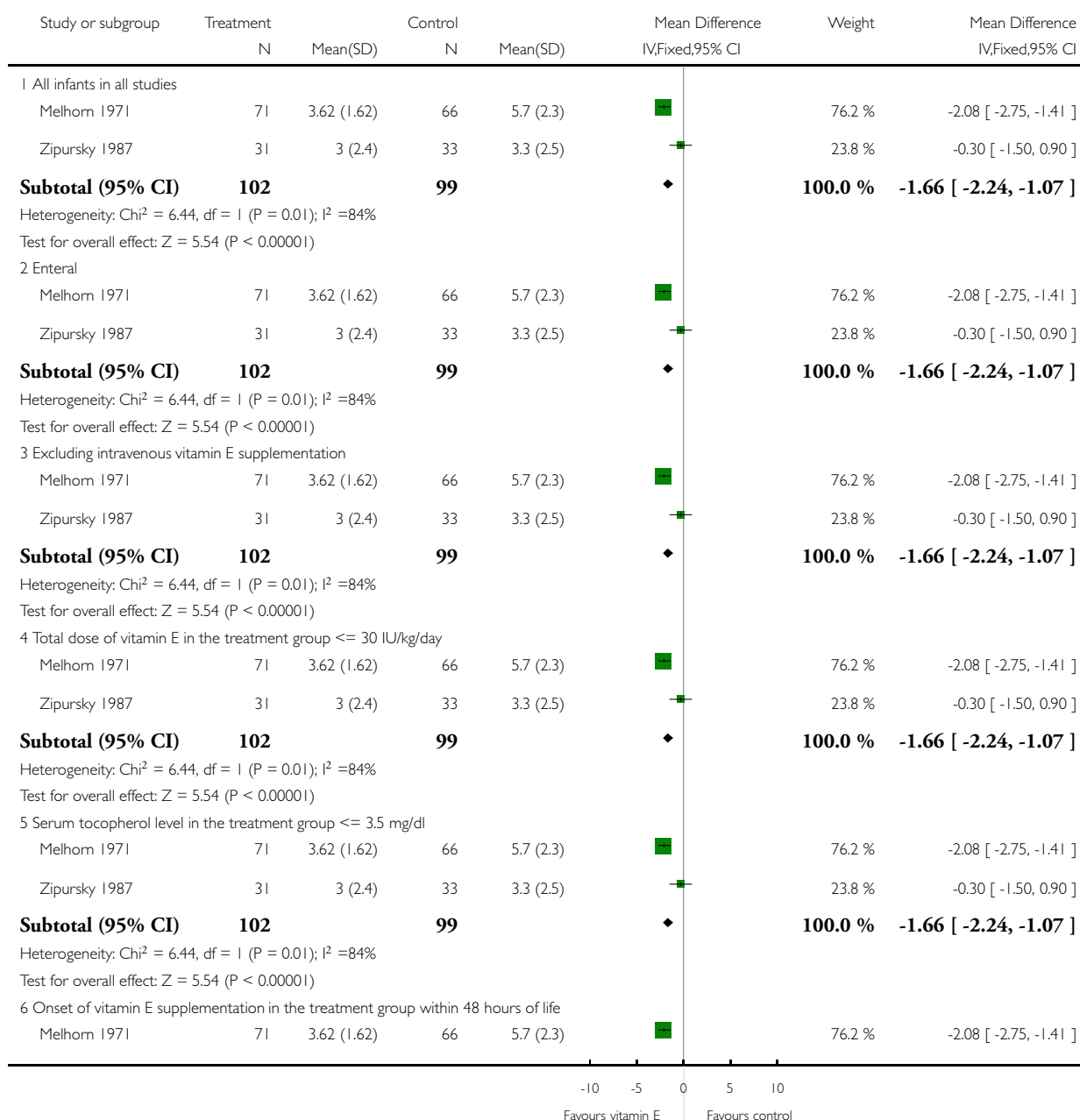


# Analysis I.54. Comparison I Vitamin E versus placebo or no vitamin E, Outcome 54 Reticulocyte count (%).

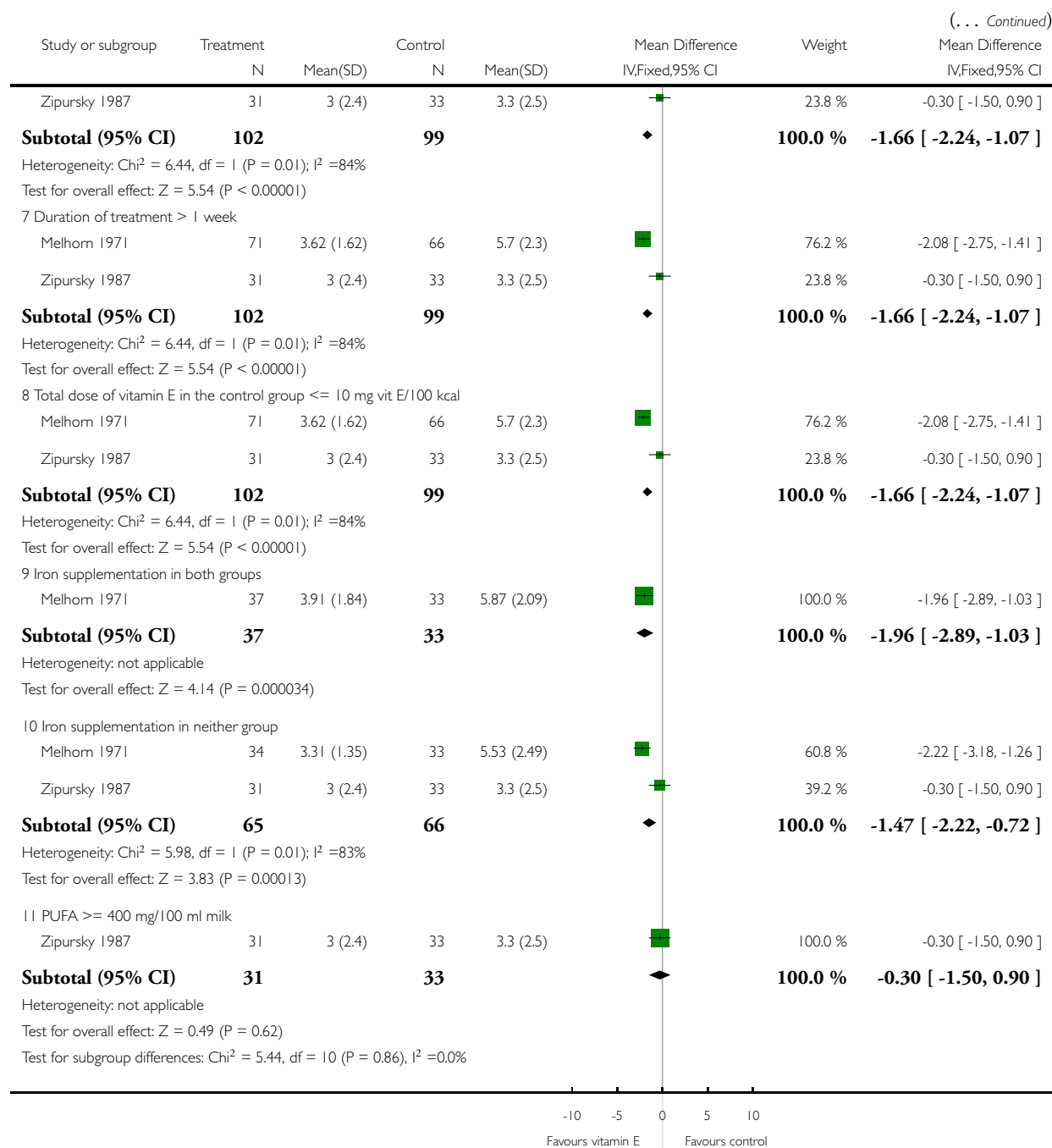
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: I Vitamin E versus placebo or no vitamin E

Outcome: 54 Reticulocyte count (%)



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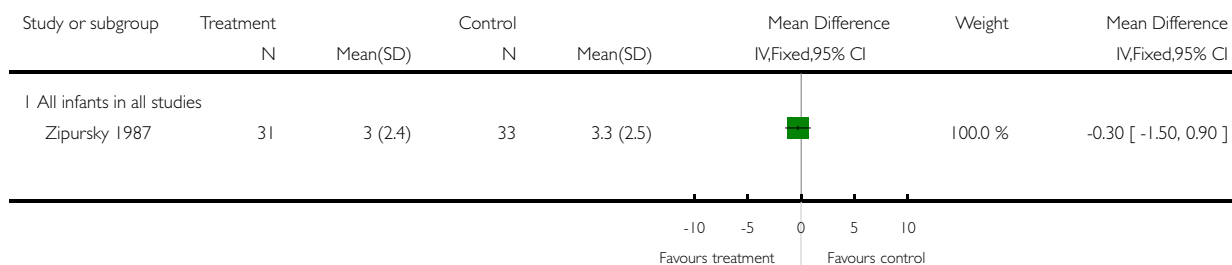


### Analysis 1.55. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 55 Reticulocyte count (%) in very low birth weight infants.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 55 Reticulocyte count (%) in very low birth weight infants

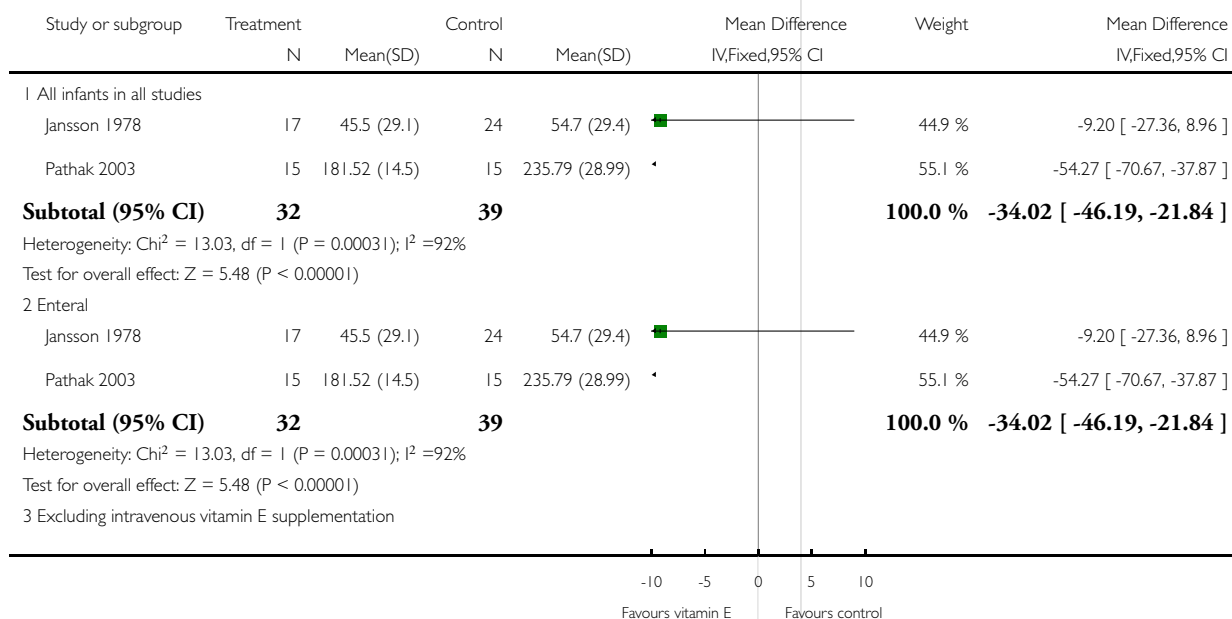


### Analysis 1.56. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 56 Reticulocyte count (million per liter).

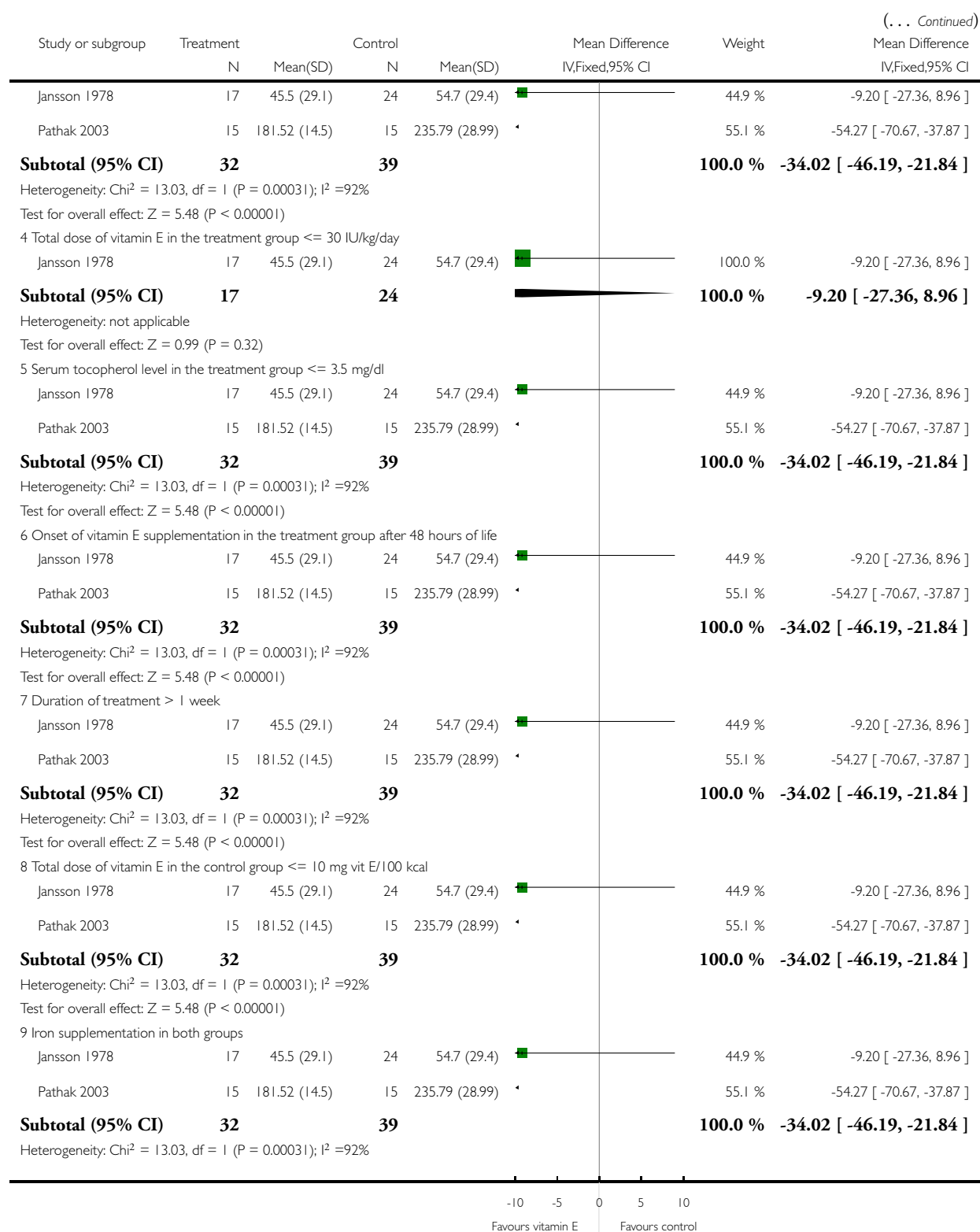
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

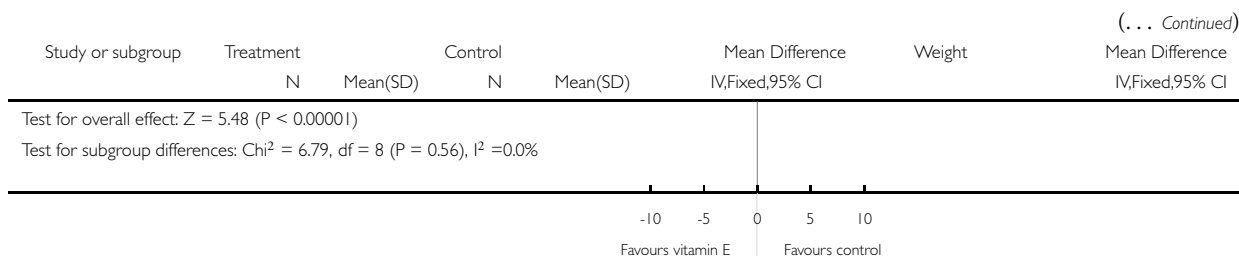
Outcome: 56 Reticulocyte count (million per liter)



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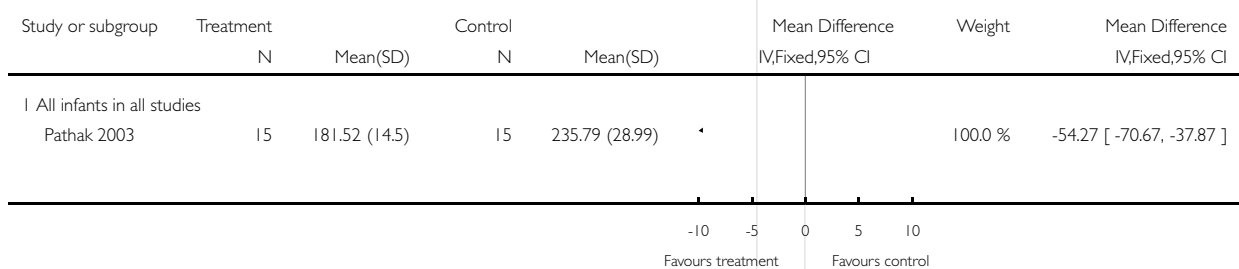


**Analysis 1.57. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 57 Reticulocyte count (million per liter) in very low birth weight infants.**

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 57 Reticulocyte count (million per liter) in very low birth weight infants

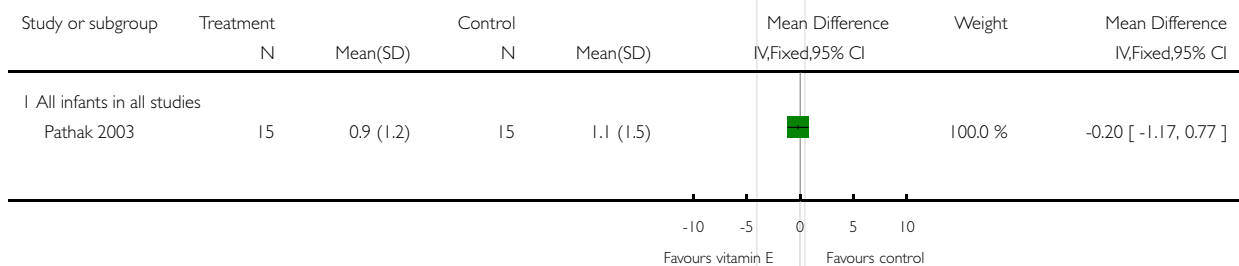


**Analysis 1.58. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 58 Number of transfusions.**

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 58 Number of transfusions

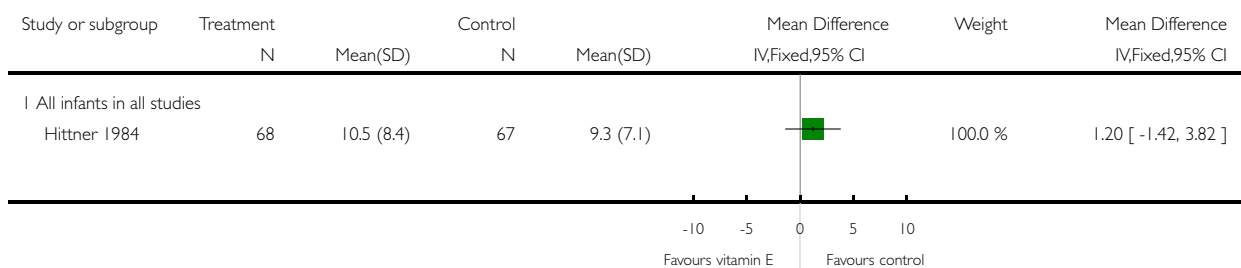


### Analysis 1.59. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 59 Number of transfusions among survivors.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 59 Number of transfusions among survivors

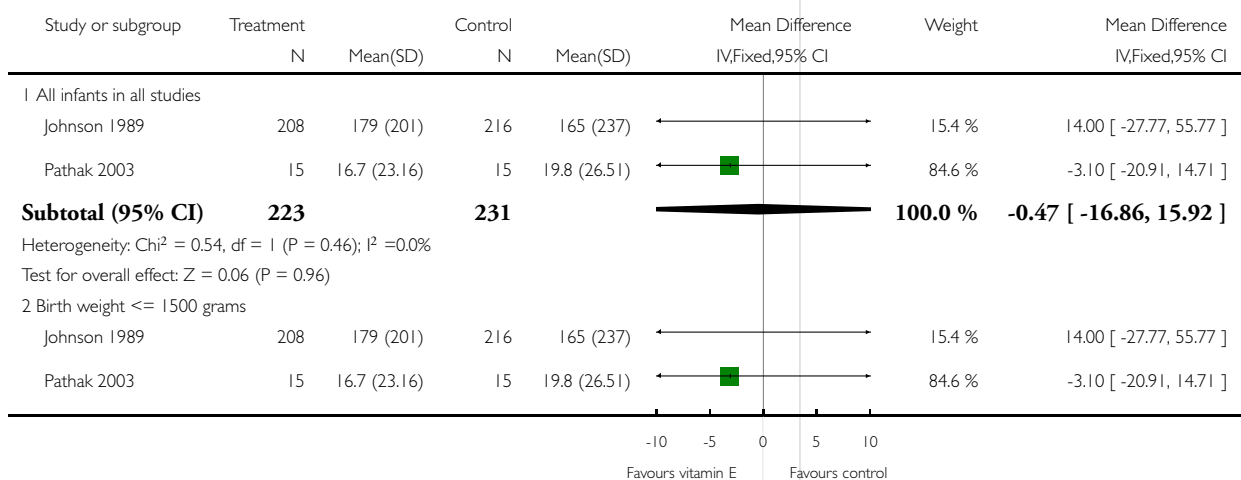


### Analysis 1.60. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 60 Amount of blood transfused (ml/kg) among very low birth weight infants.

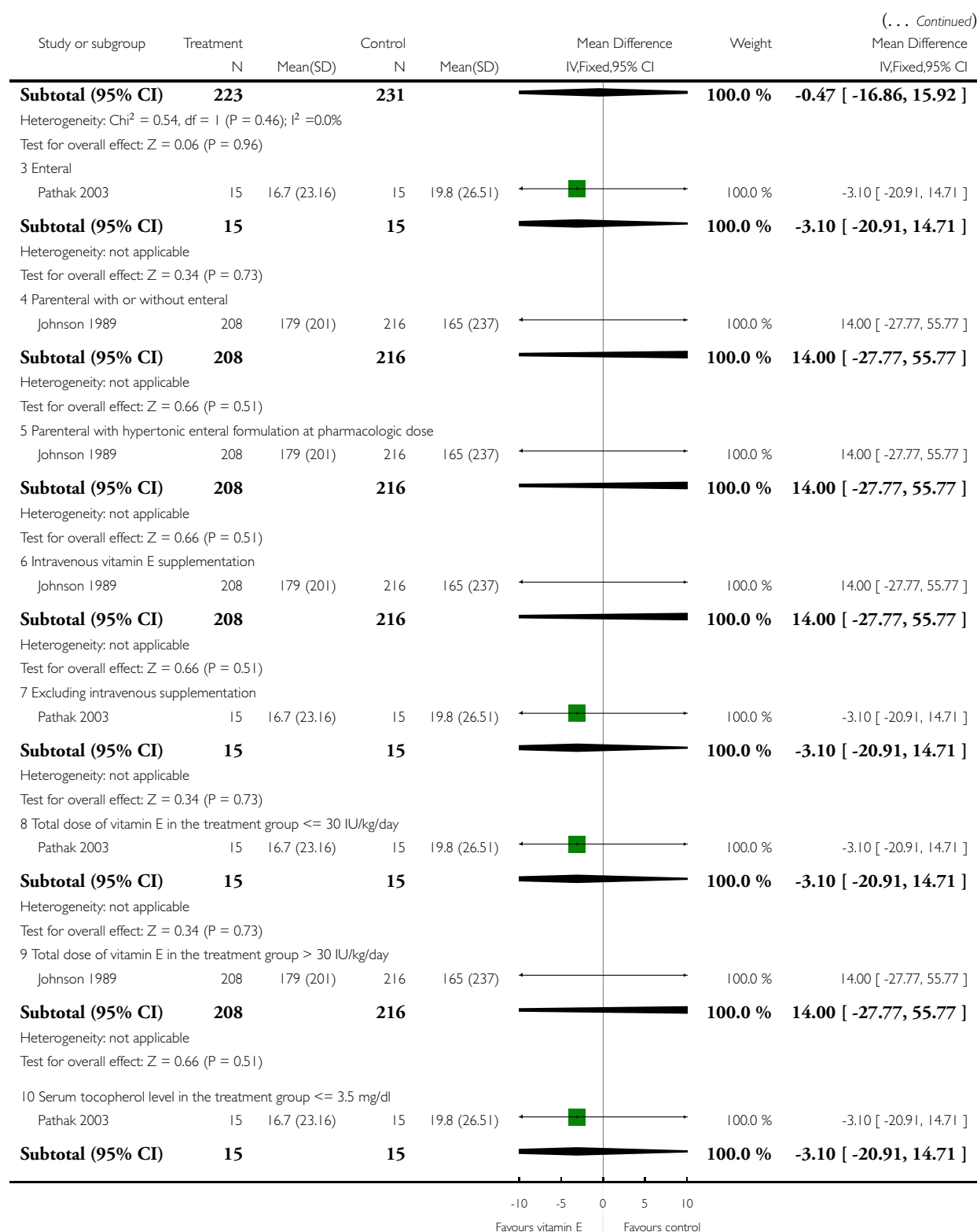
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

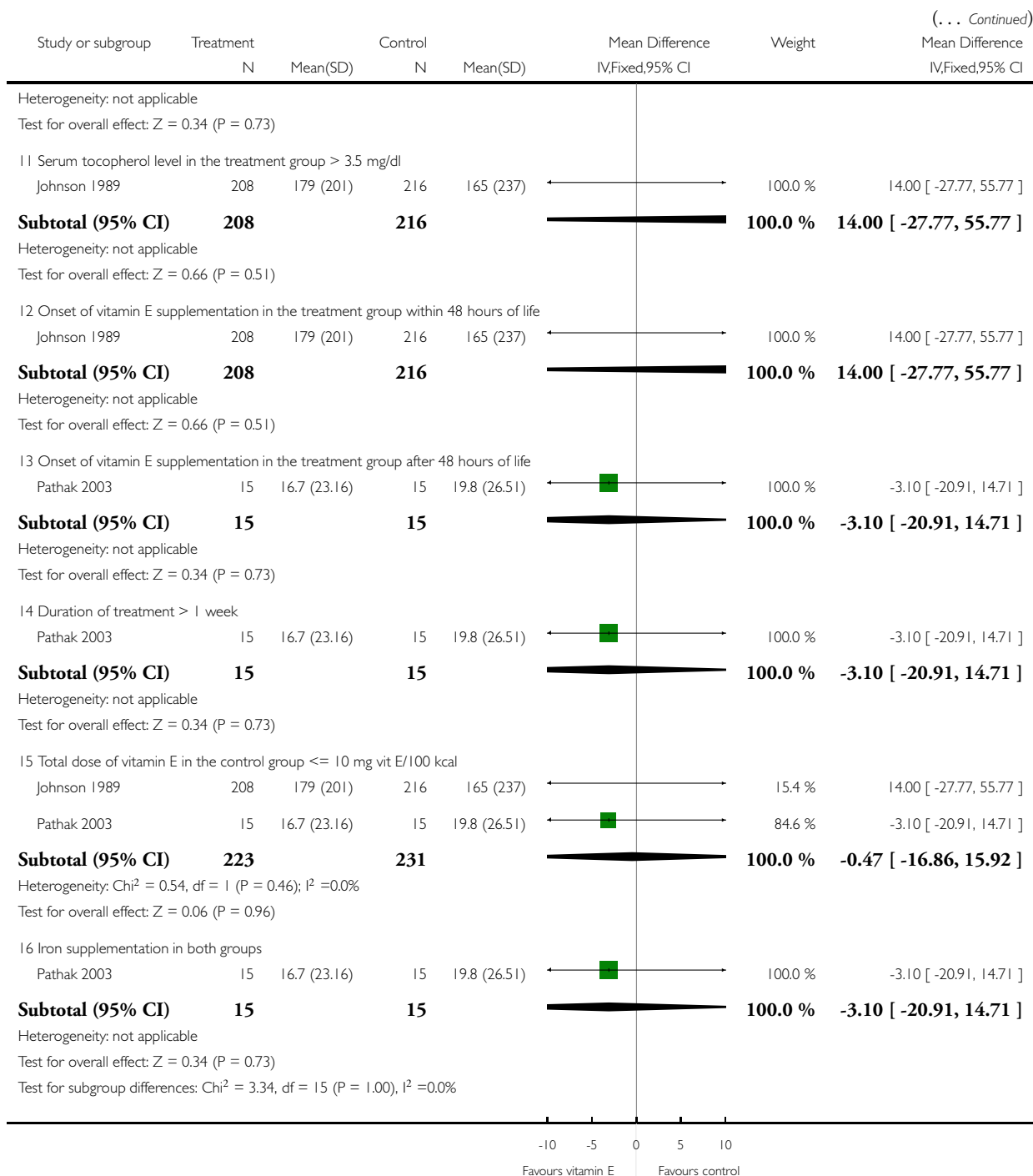
Outcome: 60 Amount of blood transfused (ml/kg) among very low birth weight infants



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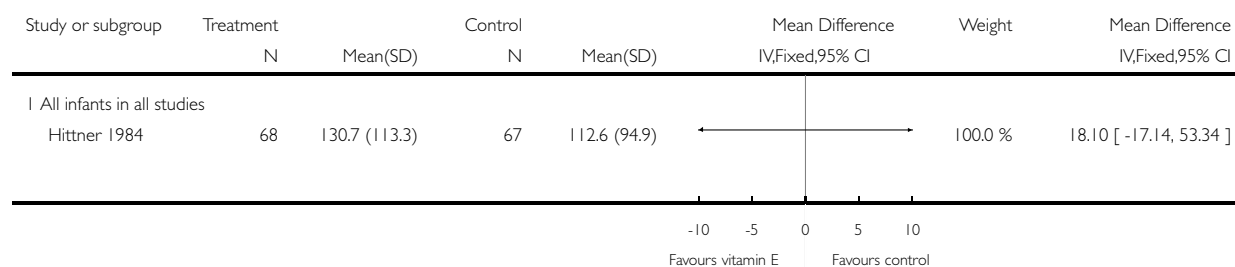


### Analysis 1.61. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 61 Amount of blood transfused (ml/kg) among surviving low birth weight infants.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 61 Amount of blood transfused (ml/kg) among surviving low birth weight infants

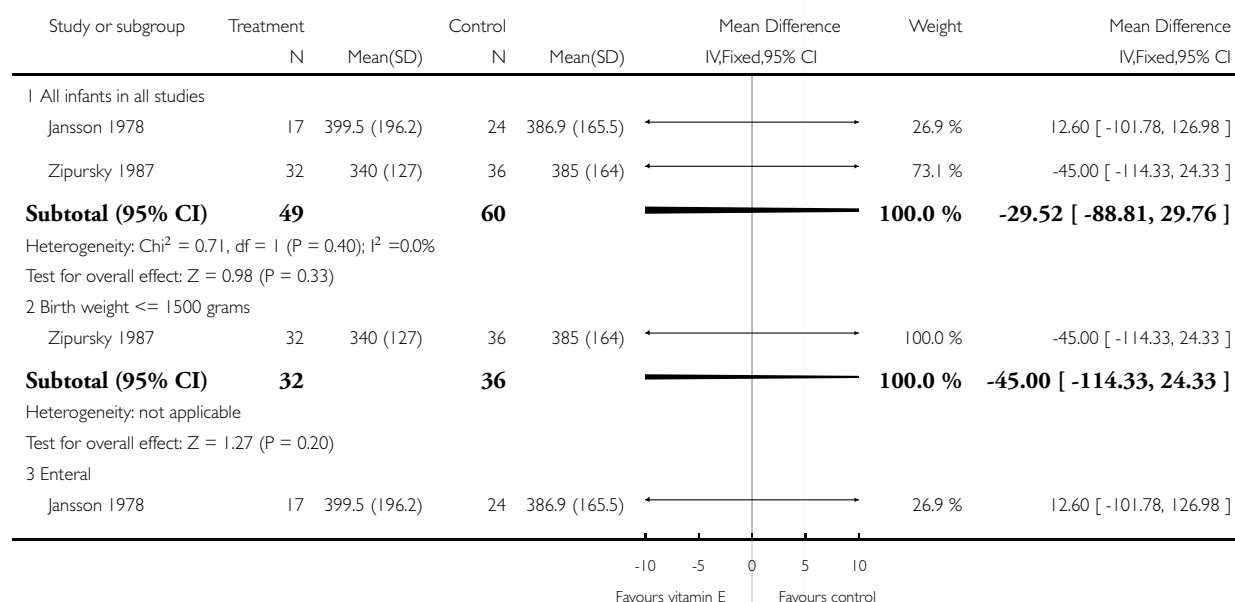


### Analysis 1.62. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 62 Platelet count (thousands/microliter).

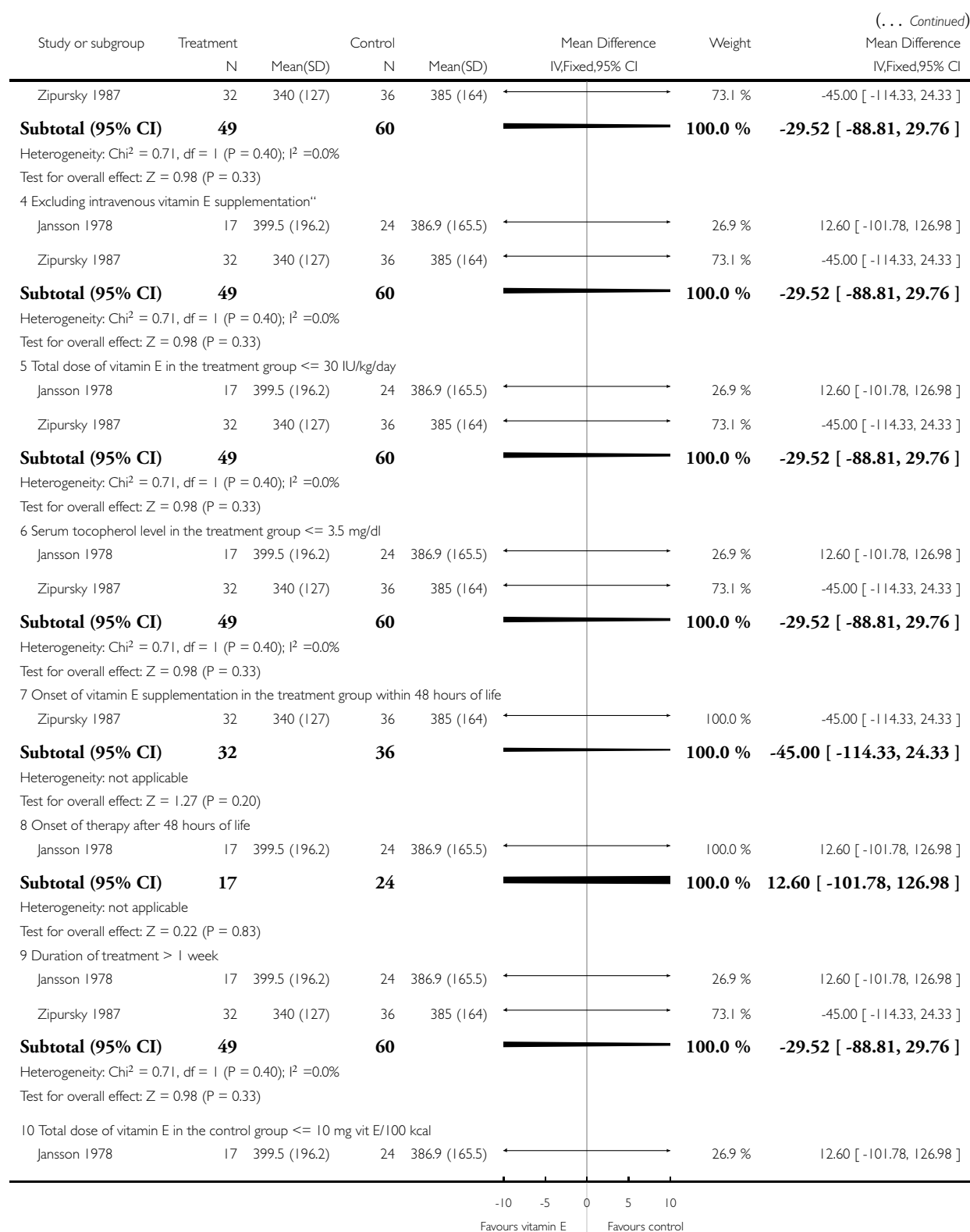
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 62 Platelet count (thousands/microliter)

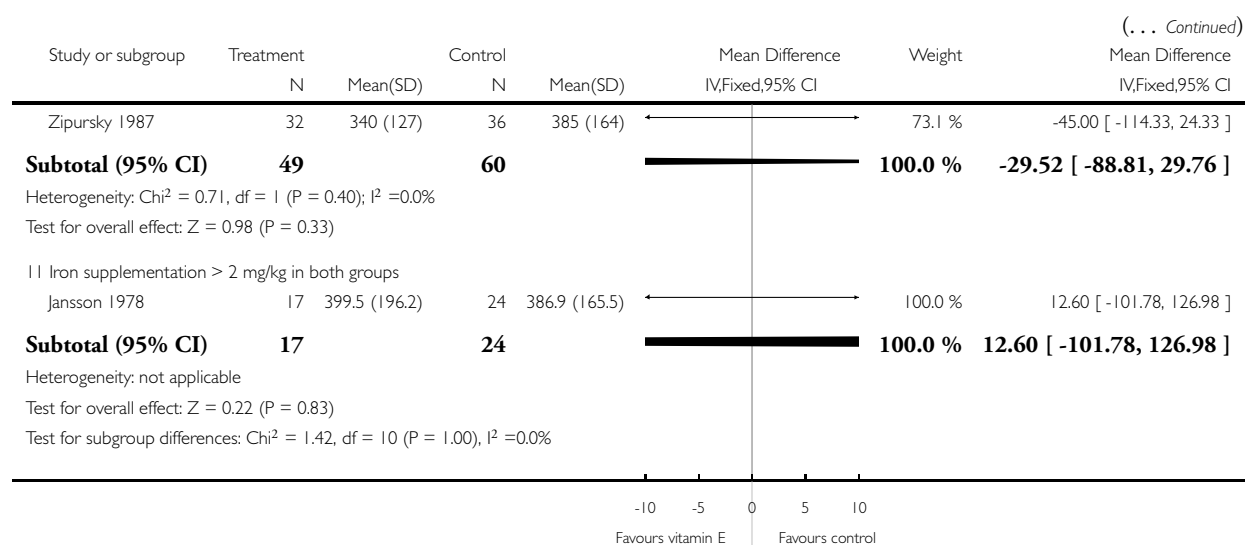


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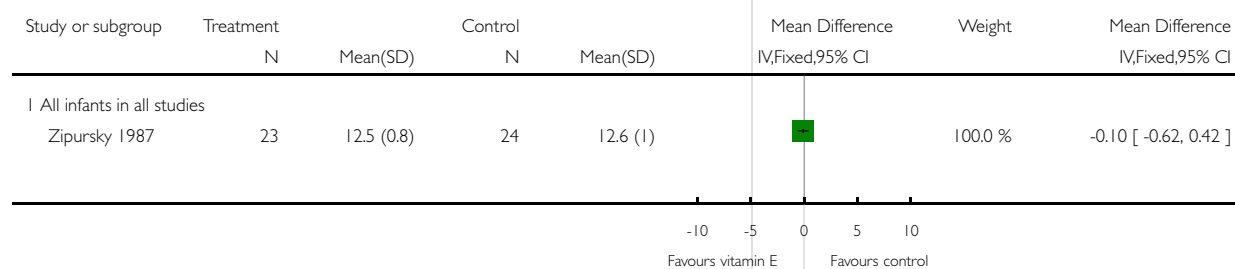


### Analysis 1.63. Comparison I Vitamin E versus placebo or no vitamin E, Outcome 63 Prothrombin time (PT, seconds).

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: I Vitamin E versus placebo or no vitamin E

Outcome: 63 Prothrombin time (PT, seconds)

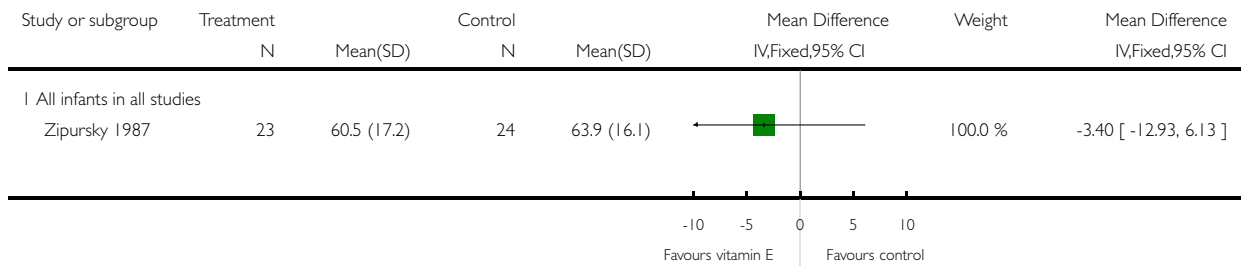


### Analysis 1.64. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 64 Partial thromboplastin time (PTT, seconds).

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 64 Partial thromboplastin time (PTT, seconds)

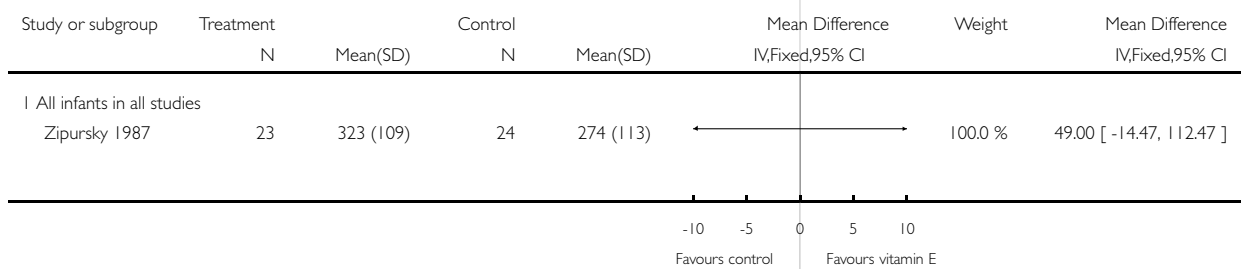


### Analysis 1.65. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 65 Fibrinogen concentration (mg/100 ml).

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 65 Fibrinogen concentration (mg/100 ml)

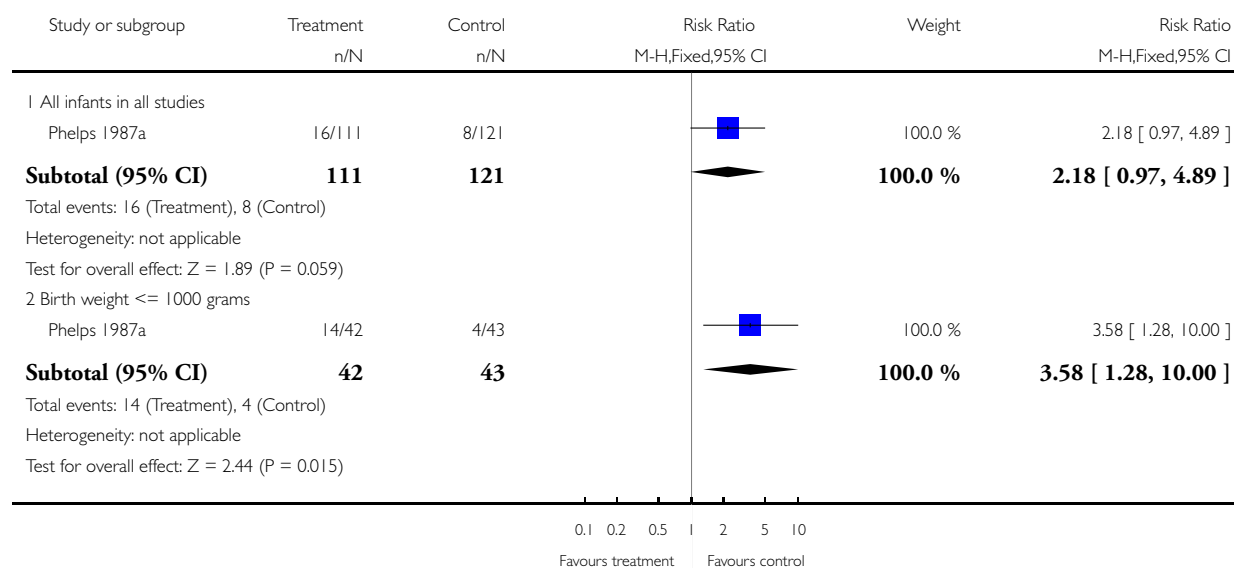


# **Analysis 1.66. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 66 Retinal hemorrhage among very low birth weight infants examined/surviving.**

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 66 Retinal hemorrhage among very low birth weight infants examined/surviving

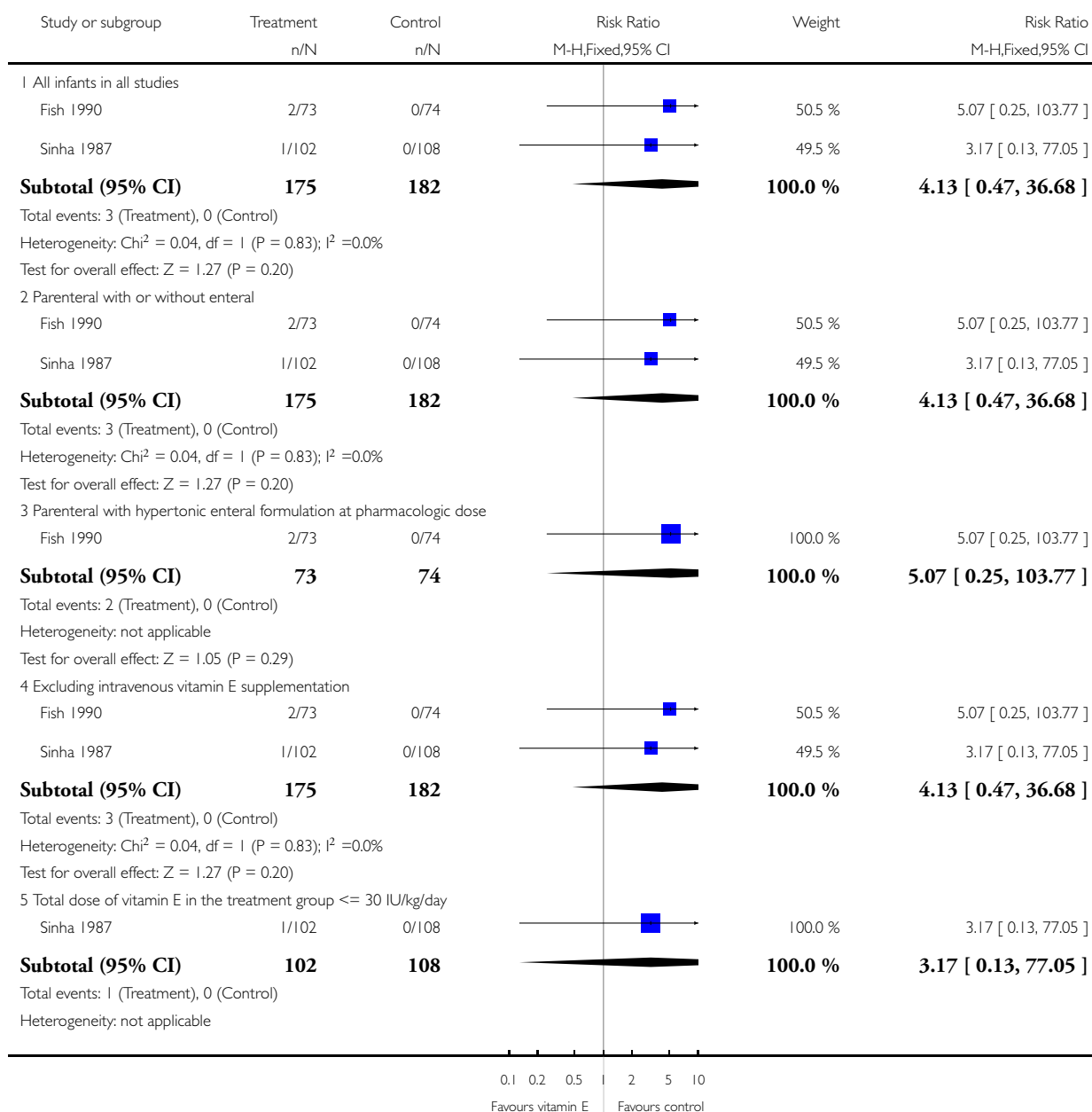


# **Analysis 1.67. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 67 Reaction at site of injection.**

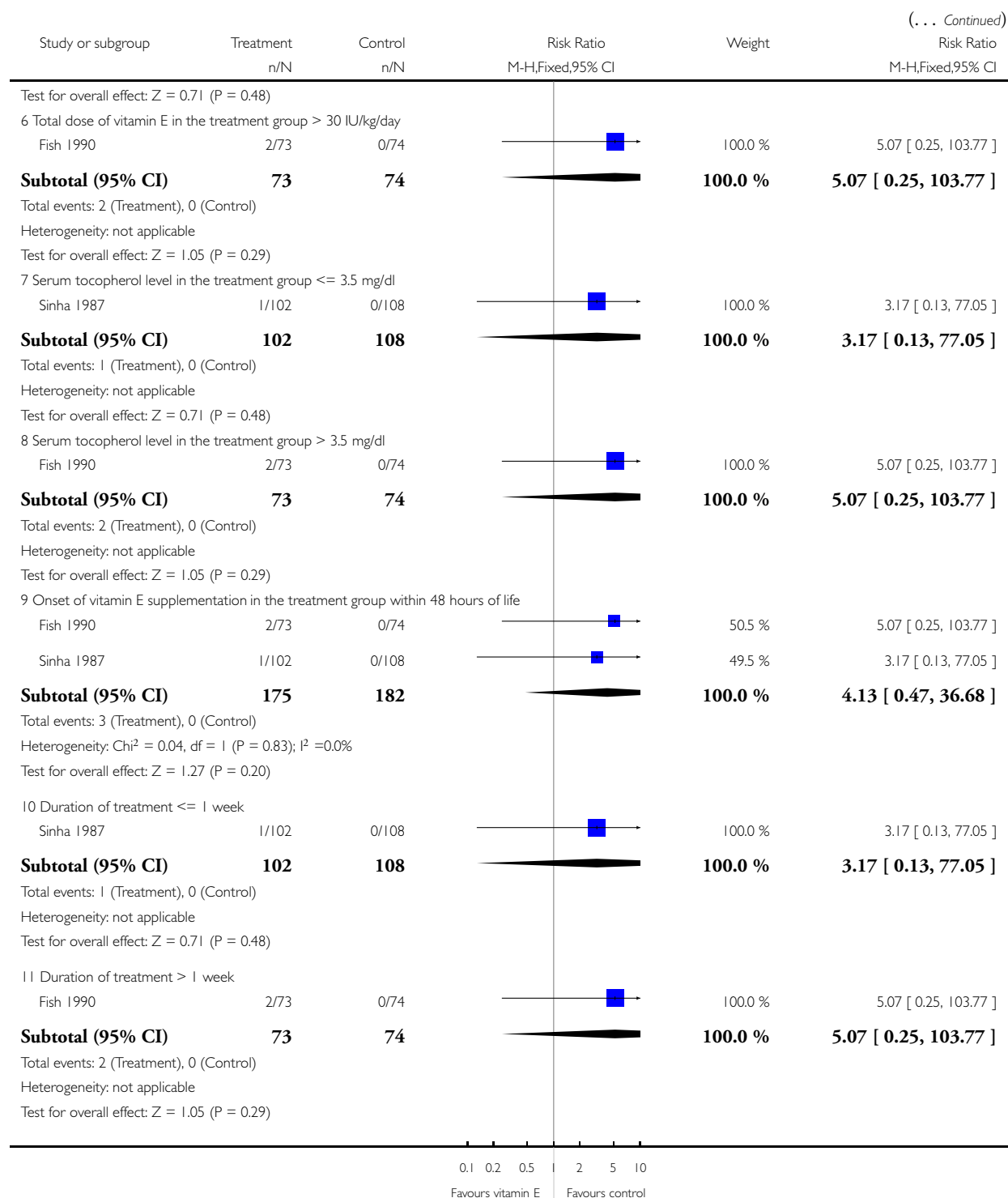
Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 67 Reaction at site of injection



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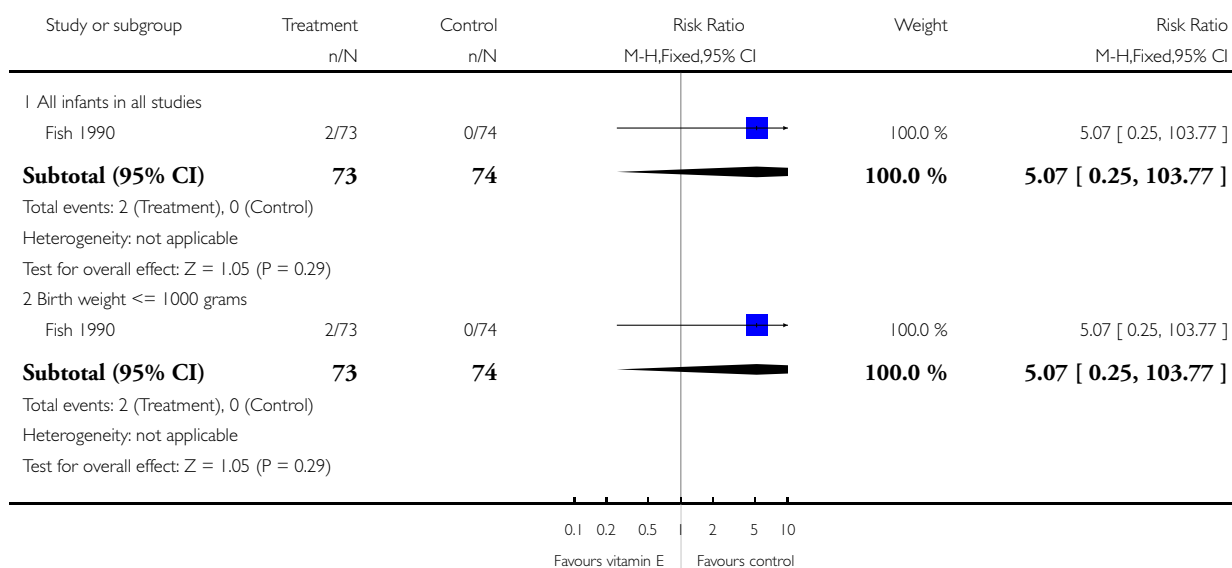


### Analysis 1.68. Comparison 1 Vitamin E versus placebo or no vitamin E, Outcome 68 Reaction at site of injection in very low birth weight infants.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 1 Vitamin E versus placebo or no vitamin E

Outcome: 68 Reaction at site of injection in very low birth weight infants

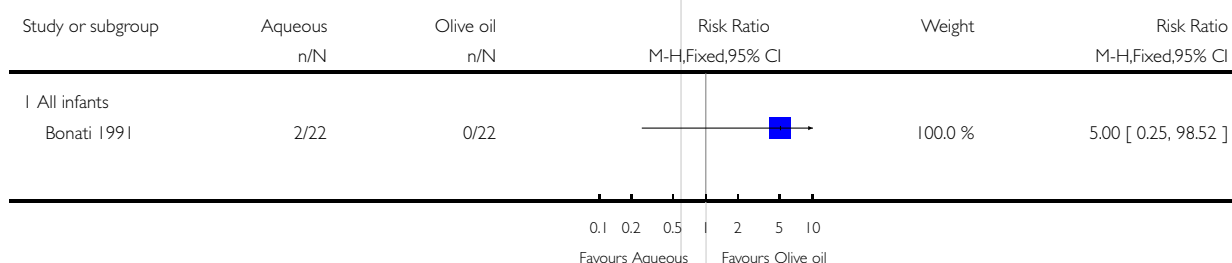


### Analysis 2.1. Comparison 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil), Outcome 1 Mortality.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome: 1 Mortality

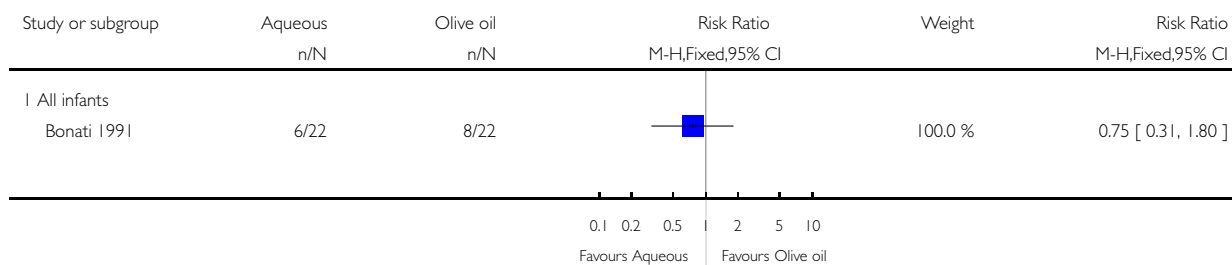


## Analysis 2.2. Comparison 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil), Outcome 2 Bronchopulmonary dysplasia.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome: 2 Bronchopulmonary dysplasia

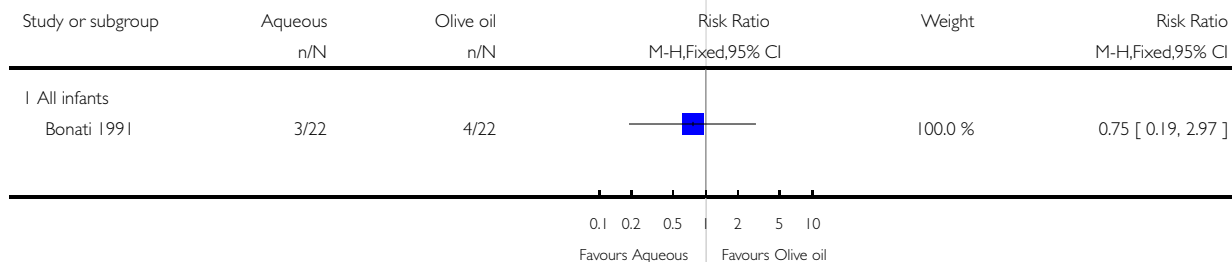


## Analysis 2.3. Comparison 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil), Outcome 3 Patent ductus arteriosus.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome: 3 Patent ductus arteriosus

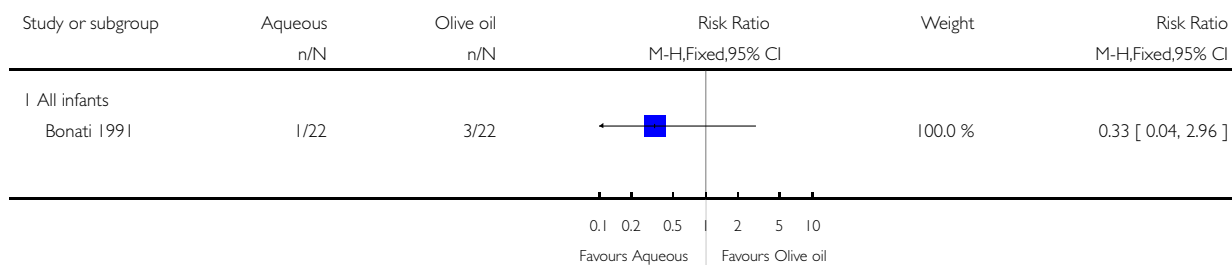


#### Analysis 2.4. Comparison 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil), Outcome 4 Sepsis.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome: 4 Sepsis

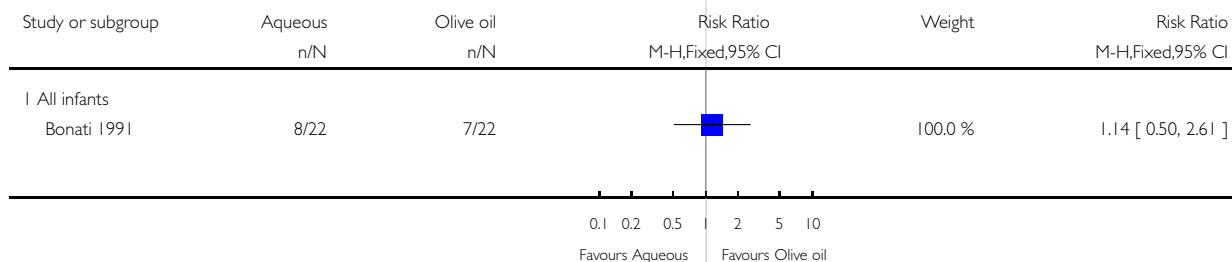


#### Analysis 2.5. Comparison 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil), Outcome 5 Germinal matrix-intraventricular hemorrhage.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome: 5 Germinal matrix-intraventricular hemorrhage



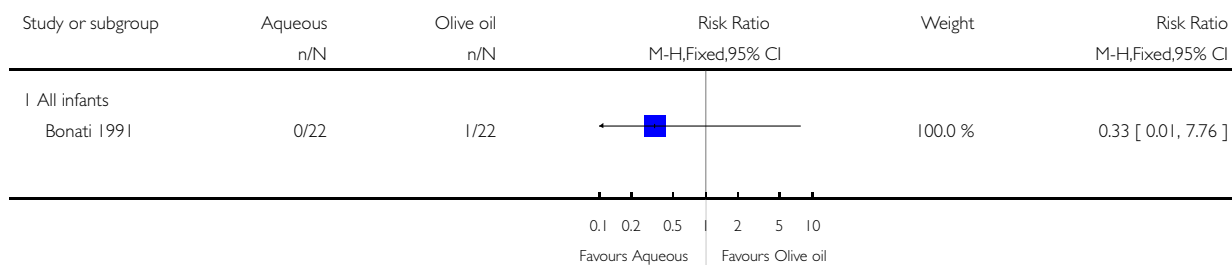


### Analysis 2.6. Comparison 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil), Outcome 6 Stage IV (intraparenchymal) intraventricular hemorrhage.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome: 6 Stage IV (intraparenchymal) intraventricular hemorrhage

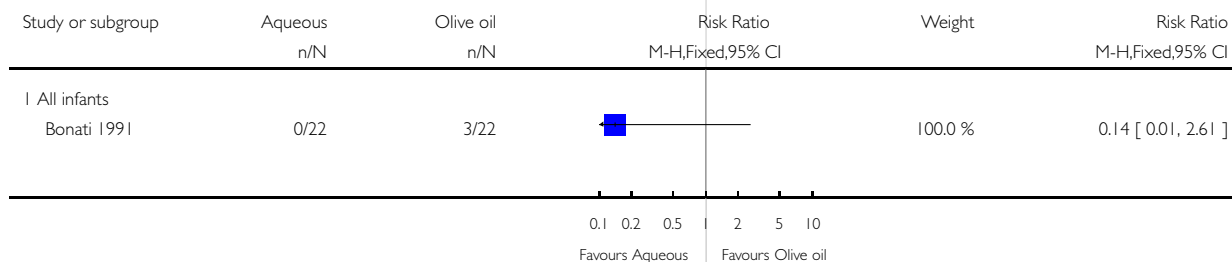


### Analysis 2.7. Comparison 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil), Outcome 7 Necrotizing enterocolitis.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome: 7 Necrotizing enterocolitis

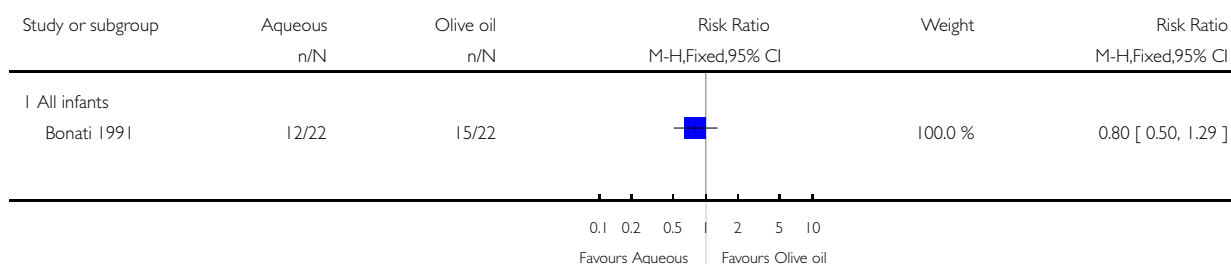


## Analysis 2.8. Comparison 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil), Outcome 8 Exchange transfusion.

Review: Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

Comparison: 2 Vitamin E (aqueous colloidal) versus another form of vitamin E (olive oil)

Outcome: 8 Exchange transfusion



## WHAT'S NEW

Last assessed as up-to-date: 30 March 2007.

20 May 2008	Amended	Converted to new review format.
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## HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 4, 2003

31 March 2007	New search has been performed	This updates the review "Vitamin E supplementation for prevention of morbidity and mortality in preterm infants" published in The Cochrane Library, Issue 4, 2003 (Brion 2003).  A repeated Medline search in March 2007 and a search of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2007, yielded one additional retrospective study (Liu 2005) and another study that is now listed in the background section (Scholl 2006). One study (Pathak 2003), in press at the time of the original version of this review, has been published.
12 June 2003	New citation required and conclusions have changed	Substantive amendment

## DECLARATIONS OF INTEREST

None

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Infant, Premature; \*Infant, Very Low Birth Weight; Antioxidants [\*administration & dosage]; Infant, Newborn; Infant, Premature, Diseases [\*mortality; \*prevention & control]; Morbidity; Randomized Controlled Trials as Topic; Vitamin E [\*administration & dosage]

### MeSH check words

Humans